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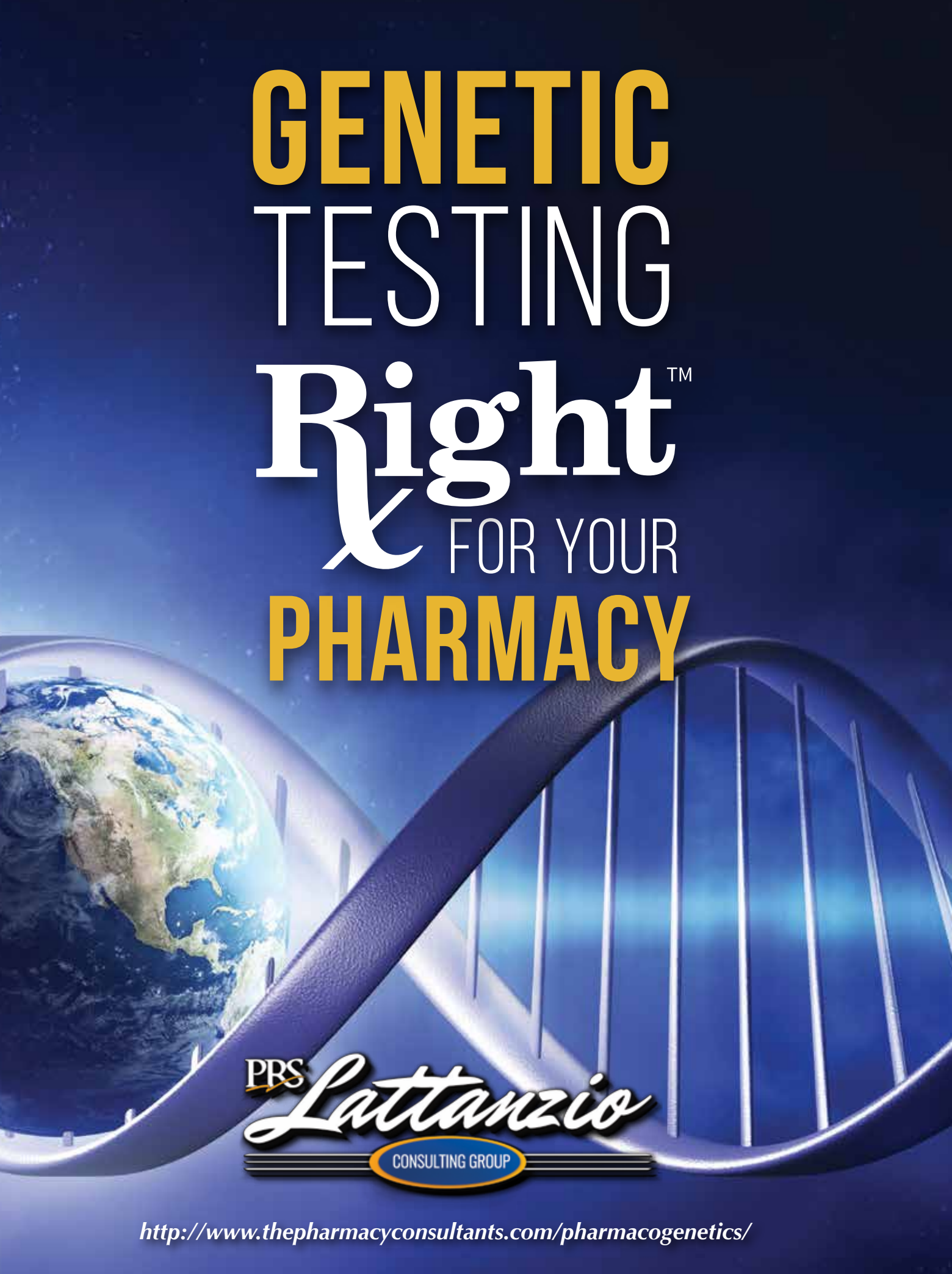

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contents

Letters to the editor—If you would like to comment on an article, email NCPA at info@ncpanet.org. Your letter may be posted on the NCPA website and edited for length and clarity.

FEATURES

THIS MONTH'S *cover* FEATURE

Caption: In the past six years, Live Oak Bank has helped community pharmacists start, build, or expand their businesses with more than 600 loans totaling $650 million. Meanwhile, the industry evolved, health care plans and providers saw radical change, and the technology revolution arrived for pharmacies. With challenges facing the transition of legacy pharmacies (such as predatory chains and reduced reimbursements), Live Oak brought a laser focus to pharmacy lending.

DEPARTMENTS

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Ask Your Family Pharmacist®

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NCPA NATIONAL COMMUNITY PHARMACISTS ASSOCIATION

The National Community Pharmacists Association (NCPA®) represents the interests of America's community pharmacists, including the owners of more than 22,000 independent community pharmacies. Together they represent an $81.4 billion health care marketplace and employ more than 314,000 individuals on a full or part-time basis. To learn more, go to www.ncpanet.org, visit facebook.com/commpharmacy, or follow NCPA on Twitter @Commpharmacy.

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Striking Back Against Underwater MAC Attacks

Independent community pharmacists around the country are reporting repeated financial losses filling Medicare Part D prescriptions. I'm hearing about it from NCPA members and also seeing it at my two pharmacies in Buffalo, N.Y. Recently I filled a prescription for Estradiol .05 mg patches where the ingredient cost was $65.95 to put on my shelf. For my investment and professional services, I received $55.33 from the PBM.

That's not right, and NCPA is working to change that dynamic. We have repeatedly contacted the Centers for Medicare & Medicaid Services and asked it to take action to compel Part D plans and/or their PBMs to comply with a federal requirement that Medicare prescription drug reimbursement reflect "the market price of acquiring the drug."

In a recent letter we expressed "our concerns and those of our members regarding the non-compliance of multiple Part D plans and PBMs regarding the usage of drug pricing standards that are used to reimburse Medicare pharmacies that clearly do not reflect 'the market price of acquiring the drug'—in direct violation of federal statute." On Jan. 1, a new CMS requirement took effect that requires plan sponsors/PBM corporations to regularly update and disclose so-called maximum allowable cost (MAC) pricing benchmarks used to determine reimbursement for community pharmacies filling Medicare prescriptions, at least every seven days. The requirement was implemented by CMS in response to concerns we raised over many months regarding below-cost payments to pharmacies using MAC values that were not updated to reflect market costs.

> ***It's outrageous that Medicare seniors' access to needed medication and the continued viability of independent community pharmacies are both being undermined by the practices of some PBM corporations and drug plan sponsors that appear to clearly conflict with federal requirements.***

So far in 2016, there have been multiple Part D plans and PBMs that have been utilizing MAC drug pricing values that are "far below what would be considered to be reasonably approaching market prices for drugs," the letter noted, and "pharmacies are dispensing these medications to seniors at significant financial losses."

Part D plans and PBMs are manipulating MAC pricing standards "as a proprietary variable that can be changed on a whim with no relation whatsoever" to real world costs, our letter said, calling that practice a "blatant disregard" for federal requirement that "is serving to undermine" the Part D program and "truly jeopardizes the ability of pharmacies to serve these patients." The practice calls into question the accuracy of drug pricing information beneficiaries rely on via the Medicare Plan Finder website as well.

It's outrageous that Medicare seniors' access to needed medication and the continued viability of independent community pharmacies are both being undermined by the practices of some PBM corporations and drug plan sponsors that appear to clearly conflict with federal requirements. We strongly urged Medicare officials to take quick action to address this problem. We will continue to engage with Medicare, Congress, and others to try and achieve a resolution of this serious problem. ■

Best,

Bradley J. Arthur, RPh
NCPA President 2015–16

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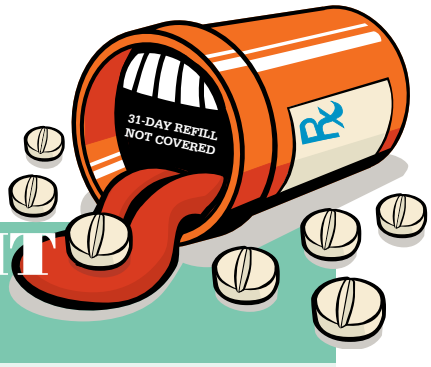
PCCA 35 YEARS

Zika: What You Need to Know

Zika is a disease caused by the Zika virus, which is spread to people primarily through the bite of an infected Aedes mosquito. The most common symptoms are fever, rash, joint pain, and conjunctivitis, says the Centers for Disease Control & Prevention. The illness is usually mild with symptoms lasting for several days to a week. People usually don't get sick enough to go to the hospital, and they very rarely die of Zika. Many people do not realize they have been infected. However, Zika virus infection during pregnancy can cause the serious birth defect microcephaly, as well as other severe fetal brain defects. For extensive information for health care professionals and the public, go to www.cdc.gov/Zika. The NACDS Foundation has a Zika prevention initiative including a one-hour webinar. ■



THE AUDIT ADVISOR

Cycle Fill Prescriptions and Audits

Q: What is the best way to cycle fill a prescription to avoid an audit?

A: Cycle filling can be done for a variety of reasons. We have seen results recently from SCIO where the pharmacies were cycle filling by month and rotating between 30 and 31 day supplies. The problem came when SCIO audited the prescriptions and found that the prescriber had only written a 30-day supply order. The other scenario that we have also seen is the same cycle filling 30/31 day supplies. This time the prescriptions were written to cover 31 day supplies, but the pharmacies consistently billed for 30 day supplies even though they were dispensing enough medication to cover a 31-day supply every other month. In both cases SCIO recouped a one-day supply for the 31 days months, which may not seem like a lot but quickly adds up.

PAAS wants to remind you that if you are going to cycle fill, make sure that you have a prescription that will cover the largest amount you would bill and that you are billing the correct day supply every month to avoid recoupments.

By Mark Jacobs, RPh, PAAS National, the Pharmacy Audit Assistance Service. For more information call 888-870-7227 toll-free, or visit www.paasnational.com.

Independent Pharmacy Today

Pharmacies using workflow technology

28% automated dispensing system

43% mobile commerce/ signature capture

40% telephone IVR

82% point-of-sale

48% automated dispensing counter

Source: 2015 *NCPA Digest*, sponsored by Cardinal Health

ADVOCACY ALERT

- **Congressional Pharmacy Summit:** More than 300 NCPA advocates carried community pharmacy's legislative solutions to **250** Capitol Hill offices, presenting hometown patient and business concerns personally to elected officials in Washington, D.C.
- **Student Advocates:** NCPA student members were well represented at the Summit, including 15 each from Auburn and Ohio Northern universities and 11 from Massachusetts College of Pharmacy and Allied Health Sciences. A special shout out goes to Athena Borhauer and Stephanie Ramirez, who made the trip to D.C. from the University of Hawaii at Hilo. Mahalo.
- **Keep the paper—for now:** NCPA and other industry stakeholders have asked Congress to bar the Food & Drug Administration from issuing a **rule** that would require pharmacists and other health care professionals to distribute prescribing information electronically until such time as Congress enacts a **law** requiring its distribution. NCPA is working to ensure that costs are not shifted to community pharmacies.
- **PBM Transparency:** For the second time in two years, Oklahoma has enacted a PBM transparency law. The **tougher 2016 version** was needed because PBMs basically ignored the first law. In the past three years, 30 states have enacted PBM transparency measures.
- **Office Use Compounding Ban?:** Rep. Buddy Carter (R-Ga.), the only pharmacist in Congress, said in a recent House floor speech that the Food & Drug Administration was **"over reaching"** and **"ignoring congressional intent"** by trying to restrict office use compounding by community pharmacies. NCPA is working with Carter and other pharmacy champions to see that state pharmacy boards continue to oversee traditional office use compounding.

Iowa's NCPA Congressional Pharmacy Summit advocates meeting with Sen. Charles E. Grassley (R-Iowa).

Asthma, Allergies, and Birth Control

Teach patients to always replace the cap on the inhaler after use.

ALWAYS INSPECT INHALER FOR FOREIGN OBJECTS BEFORE USE

When teaching patients about proper inhaler use, be sure to emphasize how important it is to recap the device after use. The importance of replacing caps was illustrated in an April 2015 BMJ case report. A woman who had asthma accidentally inhaled a small earring while using her asthma medication. She got her uncapped inhaler from her purse. As she inhaled the medication, she felt a painful scratch in her throat and started coughing blood. She was taken to the emergency department, where the earring was removed from her lung. If the inhaler's cap had been in place, the loose earring in her purse would not have gotten into the inhaler.

Another event was reported in April 2015 in England. A woman used her inhaler and suddenly felt something shoot to the back of her throat. She began gasping for air and spitting up blood. She ran outside, and a neighbor came to her rescue and called emergency medical services. The woman eventually coughed out a fake nail that had been part of a set she had worn weeks earlier. In this case, the inhaler's cover had been in place before use, so the nail had probably lodged in the inhaler while using it when wearing the nails.

Tell patients to always inspect the inhaler thoroughly before use to ensure that there are no unwanted objects within the inhaler. Also advise them to replace the inhaler cap after every use. If a foreign object enters the inhaler, it places the person at risk of breathing in the object and causing choking or respiratory difficulties.

SEASONALE OR SEASONAL?

Inaccurate or inappropriate allergies may be documented in health records when patients report "seasonal allergies." SEASONALE, the brand name of an oral contraceptive containing levonorgestrel and ethinyl estradiol, has been accidently selected in the allergy field when the intention was to document seasonal allergies. The Institute for Safe Medication Practices received a report of a persistent problem with providers selecting this choice. Their system records only actual substances (such as pollen, birch) to which a patient is allergic. "Seasonal" is not a choice, but staff see Seasonale listed and select it, believing they've found the right term. Thus, inaccurate allergy information is recorded, and the patient might be mistakenly identified with a birth control pill allergy in her medical record.

A similar situation happened in a health care facility. A patient reported that she had seasonal allergies. The nurse typed "seasonal" into the allergy field of the physician office's electronic health record without realizing that the system converted it to Seasonale. Later, upon admission to a hospital, a medication reconciliation technician asked the patient about her allergy to Seasonale and learned that the patient did not have a uterus and had no need for the contraceptive, but she did experience seasonal allergies. In this case, no harm occurred, but one can imagine a scenario where a patient's oral contraceptive or hormone replacement therapy is never prescribed, or is discontinued inappropriately, based on the incorrect allergy information.

Remind staff about potential mix-ups between Seasonale and seasonal allergies, and to never select this drug unless the patient is truly allergic to the medication. ■

This article is from the Institute for Safe Medication Practices (ISMP). The reports described were received through the USP–ISMP Medication Errors Reporting Program. Errors, near misses, or hazardous conditions may be reported on the ISMP website at www.ismp.org. ISMP can be reached at 215-947-7797 or ismpinfo@ismp.org.

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Ease a Pain Point, Gain a Customer

by Liz Tiefenthaler

On May 17, *Tech Insider* reported about a new kind of pharmacy opening in New York City. The pharmacy, called Capsule (www.capsulecares.com), states it never wants you to visit a pharmacy like Walgreens or CVS again. Instead, it will deliver your pills to your home or office for you, for free. This pharmacy has just one location and a great app, so that you can refill all of your prescriptions online and a pharmacist is always willing to speak with you.

Now check out PillPack (www.pillpack.com), another independent pharmacy start-up that simplifies the pharmacy experience by offering multi-dose strip packaging, delivered for free. And the best part is that it synchronizes your medications and makes sure they are delivered to you at the same time. All that patients pay is their insurance co-pay.

You might be thinking, "I offer free delivery and my pharmacists are always available to help a patient. Why is this different?" Now, most of you are also thinking, "I offer multi-dose packaging and I have a great synchronization program. Why is this suddenly news?" It is because the young pharmacists who are boldly starting these pharmacies have learned what the pain points are for people, and they are addressing them. Did you notice that neither one promoted their drive-thru window? And neither pharmacy gave a long list of services. No, they address one pain point – having to drive to a pharmacy and wait in line, having to make multiple trips each month to the pharmacy, and taking the confusion out of taking multiple medications. Then they explain why they are different while still offering personal and caring service. Finally, they promote the digital component of online refills with an app in one case and a great website in the other. These start-ups speak in a language the consumer can understand and make their story about how they are going to make a patient's experience better.

How often do you take the time to let patients know that you can rid their pain points for them? Sure, everyone wants fast and friendly service, but let's be honest, that is expected today. This is about taking a look at what you offer and marketing those specific services that could really impact someone's life. It doesn't matter whether you are a pharmacy or a different type of business that serves consumers, it is imperative that all businesses take a look at what they offer and make sure it is what the consumer wants. Then think about ways that you can refine your message so that it is simple to understand and simple to remember.

Take a lesson from our young and bold new independents and let patients know what you are already doing. Simplify your message, solve the patient's pain points, and watch your business grow. ■

Liz Tiefenthaler is the president of Pharm Fresh Media, a full-service marketing company focused on helping independent pharmacies gain new customers and build loyalty with their current customers. She can be reached at liz@pharmfreshmedia.com.

The name BRINTELLIX (vortioxetine) has changed to

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vortioxetine
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BRINTELLIX NDC Numbers			
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New TRINTELLIX NDC Numbers *Please link the NDC numbers in your system*			
Bottles of 30	64764-720-30	64764-730-30	64764-750-30

Tablets are not actual size.

Indication

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) in adults.

Important Safety Information

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber.

TRINTELLIX has not been evaluated for use in pediatric patients.

CONTRAINDICATIONS

Patients with hypersensitivity to vortioxetine or to any components of the TRINTELLIX formulation should not take TRINTELLIX. Angioedema has been reported in patients treated with TRINTELLIX.

Do not use an MAOI with TRINTELLIX or within 21 days of stopping TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI. Do not start TRINTELLIX in a patient being treated with linezolid or intravenous methylene blue.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk: All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, or discontinuing the medication. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients daily.**

Serotonin syndrome, potentially life-threatening, has been reported with serotonergic antidepressants (SNRIs, SSRIs, and others), including TRINTELLIX, both when used alone but especially when coadministered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and others, such as linezolid and intravenous methylene blue). If such symptoms occur, discontinue TRINTELLIX and any concomitant serotonergic agents, and initiate supportive treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation.

Activation of mania/hypomania can occur. Screen patients for bipolar disorder prior to initiating antidepressant treatment. Use cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Angle-closure glaucoma has occurred with antidepressant treatment in patients with anatomically narrow angles who did not have patent iridectomy.

Hyponatremia, which may be severe, can occur in association with syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients and patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinue TRINTELLIX in patients with symptomatic hyponatremia and initiate appropriate medical intervention.

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo in 6- to 8-week studies) were nausea, constipation, and vomiting.

Coadministration with strong CYP2D6 inhibitors or strong CYP inducers may require a dose adjustment of TRINTELLIX.

Please see Brief Summary of full Prescribing Information on the following pages.

Takeda

Lundbeck

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

TRINTELLIX (vortioxetine) tablets, for oral use

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions]*.

TRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations]*.

INDICATIONS AND USAGE

Major Depressive Disorder

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD). The efficacy of TRINTELLIX was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults.

CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with TRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Warnings and Precautions]*.

  Starting TRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases
Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRINTELLIX is not approved for use in treating bipolar depression.

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including TRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of TRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. TRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking TRINTELLIX. TRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications]*.

If concomitant use of TRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions]*.

Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with TRINTELLIX in pre-marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use TRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

Angle Closure Glaucoma

Angle Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

Hyponatremia

Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with TRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of TRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions]*
- Serotonin Syndrome *[see Warnings and Precautions]*
- Abnormal Bleeding *[see Warnings and Precautions]*
- Activation of Mania/Hypomania *[see Warnings and Precautions]*
- Hyponatremia *[see Warnings and Precautions]*

Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

TRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-marketing clinical studies; 2616 of those patients were exposed to TRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to TRINTELLIX in a 24 week to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12-month open-label studies. A total of 2586 patients were exposed to at least one dose of TRINTELLIX in open-label studies, 1727 were exposed to TRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in MDD patients treated with TRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any TRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2. Common Adverse Reactions Occurring in ≥2% of Patients Treated with any TRINTELLIX Dose and at Least 2% Greater than the Incidence in Placebo-treated Patients

System Organ Class Preferred Term	TRINTELLIX 5 mg/day	TRINTELLIX 10 mg/day	TRINTELLIX 15 mg/day	TRINTELLIX 20 mg/day	Placebo
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

*includes pruritus generalized

Nausea

Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was 2 weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of TRINTELLIX treatment with 15 to 20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking TRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MDD 6 to 8 week controlled trials of TRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3) ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with TRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	**TRINTELLIX 10 mg/day** N=94:86†	**TRINTELLIX 15 mg/day** N=57:67†	**TRINTELLIX 20 mg/day** N=67:59†	**Placebo** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

*Incidence based on number of subjects with sexual dysfunction during the study / number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

† Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

Adverse Reactions Following Abrupt Discontinuation of TRINTELLIX Treatment

Discontinuation symptoms have been prospectively evaluated in patients taking TRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of TRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests

TRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of TRINTELLIX *[see Warnings and Precautions]*. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12-week, open-label phase, there were no clinically important changes in lab test parameters between TRINTELLIX and placebo-treated patients.

Weight

TRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12-week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients.

Vital Signs

TRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo

Gastrointestinal disorders — dyspepsia

Nervous system disorders — dysgeusia

Vascular disorders — flushing

DRUG INTERACTIONS

CNS Active Agents

Monoamine Oxidase Inhibitors

Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs

Based on the mechanism of action of TRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when TRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if TRINTELLIX is co-administered with other serotonergic drugs. Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions]*.

Other CNS Active Agents

No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of TRINTELLIX. Multiple doses of TRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg). Details on the potential pharmacokinetic interactions between TRINTELLIX and bupropion can be found in the section titled: *Potential for Other Drugs to Affect TRINTELLIX*.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)

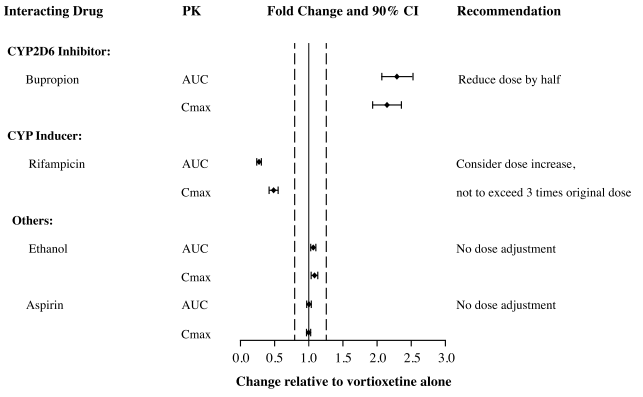
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of TRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions]*. Coadministration of aspirin 150 mg/day with multiple daily doses of TRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions]*.

Potential for Other Drugs to Affect TRINTELLIX

Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the TRINTELLIX dose when a strong CYP inducer (e.g., rifampicin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose (*Figure 1*).

Figure 1. Impact of Other Drugs on Vortioxetine PK



Potential for TRINTELLIX to Affect Other Drugs

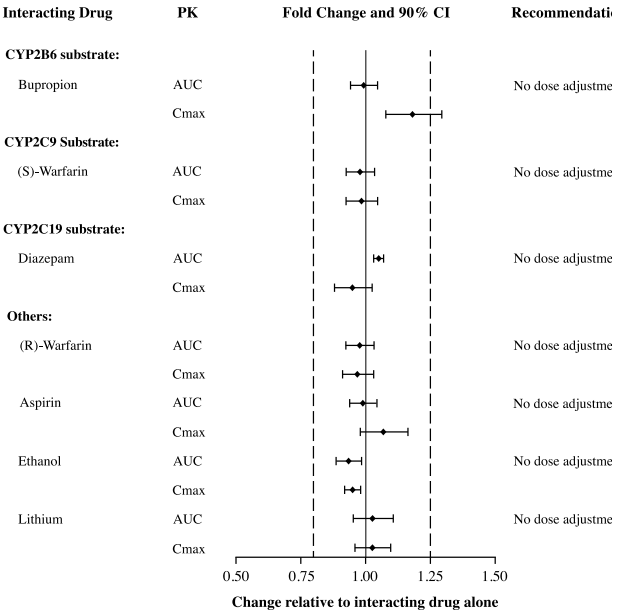
No dose adjustment for the comedications is needed when TRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinide), CYP2C9 (e.g., S-warfarin), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine), CYP3A4/5 (e.g., budesonide), and P-gp (e.g., digoxin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and P-gp. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of TRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of TRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2).*

Because vortioxetine is highly bound to plasma protein, coadministration of TRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, in a clinical study with coadministration of TRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions].*

Figure 2. Impact of Vortioxetine on PK of Other Drugs



USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of TRINTELLIX in pregnant women. Vortioxetine caused developmental delays when administered during pregnancy to rats and rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times, the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for TRINTELLIX. All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. TRINTELLIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or possibly, a drug discontinuation syndrome. It should be noted that in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*. When treating a pregnant woman with TRINTELLIX during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Neonates exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use in pregnancy and PPHN. Other studies do not show a significant statistical association.

A prospective longitudinal study was conducted of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy. When treating a pregnant woman with TRINTELLIX, the physician should carefully consider both the potential risks of taking a serotonergic antidepressant, along with the established benefits of treating depression with an antidepressant.

Animal Data

In pregnant rats and rabbits, no teratogenic effects were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses up to 120 mg/kg (58 times the MRHD) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased at 40 and 120 mg/kg. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

Nursing Mothers

It is not known whether vortioxetine is present in human milk. Vortioxetine is present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from TRINTELLIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Clinical studies on the use of TRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRINTELLIX in the pediatric population have not been established.

Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs. young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

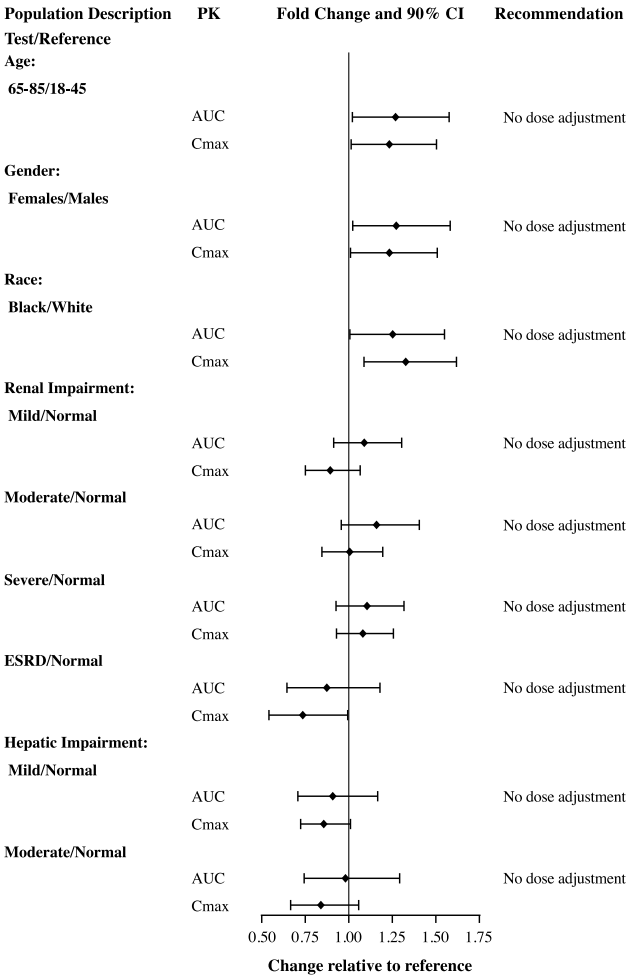
Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*.

Use in Other Patient Populations

No dose adjustment of TRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment *(Figure 3)*. TRINTELLIX has not been studied in patients with severe hepatic impairment. Therefore, TRINTELLIX is not recommended in patients with severe hepatic impairment.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



DRUG ABUSE AND DEPENDENCE

TRINTELLIX is not a controlled substance.

OVERDOSAGE

Human Experience

There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of TRINTELLIX in the dose range of 40 to 75 mg was associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

Management of Overdose

No specific antidotes for TRINTELLIX are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

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Think You've Been Overpaid? Better Find Out Within 60 Days.

by Jeffrey S. Baird, Esq.

Section 6402 of the Affordable Care Act states that any provider or supplier that receives an overpayment must report to the Centers for Medicare & Medicaid Services (CMS), and provide written notice of the reason for the overpayment. The overpayment must be reported and returned no later than 60 days after it is identified. Failure to do so may result in civil monetary penalties under the Federal False Claims Act.

In a recently released final rule, CMS has given guidance regarding the obligations of providers and suppliers to report and repay overpayments.

- The final rule addresses the "lookback period." This is the time period for which a pharmacy must examine its patient files for overpayment obligations. CMS originally proposed a 10-year lookback period. However, the final rule has shortened the lookback period to six years.
- The final rule states that, as a general rule, a provider will have six months to investigate possible overpayments before the 60-day clock starts running. Compare this to the proposed rule, which said that the investigation should be conducted with "all deliberate speed."
- The final rule addresses what it means to "identify an overpayment." Identification occurs when a provider "has or should have, through the exercise Section 6402 of the Affordable Care Act states that any provider or supplier that receives an overpayment must report to the Centers for Medicare & Medicaid Services (CMS), and provide written notice of the reason for the overpayment. The overpayment must be reported and returned no later than 60 days after it is identified. Failure to do so may result in civil monetary penalties under the Federal False Claims Act.

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- The final rule addresses what it means to "identify an overpayment." Identification occurs when a provider "has or should have, through the exercise of reasonable diligence, determined that the person has received an overpayment and quantified the amount of the overpayment." The word "quantified" is significant. In including "quantified," CMS responded to commentators who argued that an overpayment must be quantified before it can be reported and repaid. According to the final rule: "We agree and have revised the language…to clarify that part of identification is quantifying the amount, which requires a reasonably diligent investigation." The "reasonable diligence" requirement differs from the proposed rule which stated that identification occurs when a provider "has actual knowledge of the existence of the overpayment or acts in reckless disregard or deliberate ignorance of the existence of the overpayment."

Let's focus on the third bullet. Under the final rule, a pharmacy will have identified an overpayment if the pharmacy conclusively knows about it, or if the supplier would have known about it by acting with "reasonable diligence." Although the term "reasonable diligence" gives flexibility to CMS, CMS is unlikely to punish a good faith compliance effort. As stated in a recent court ruling involving the 60-day rule: "[E]nforcement actions aimed at well-intentioned health care providers working with reasonable haste to address erroneous overpayments…would be unlikely to succeed." It is important to note that the 60-day rule requires "proactive compliance activities…to monitor for the receipt of overpayments." Said another way, the pharmacy must be proactive, not reactive. Lastly, the final rule states that it is "certainly advisable" for providers to create a paper trail that serves as evidence of reasonable diligence.

Stripping all of the "legalese" away, what does this mean for the pharmacy?

- The pharmacy must be proactive, not reactive. It is not an option for the pharmacy to "bury its head in the sand."
- There may be various reasons why a pharmacy should not have received payment for a claim. For example: the provider's documentation is deficient and cannot be rehabilitated; or the claim results from actions that violate the Medicare anti-kickback statute…or the Stark physician self-referral statute…or the beneficiary inducement statute…or the telephone solicitation statute. If a claim should not have been paid to the provider, then it is likely that a person knows about it. That person might be a mid-level employee in the billing department, or an intake person, or sales rep.
- An employee who knows that a claim should not have been paid is a potential "whistleblower." If the provider engages in "reasonable diligence," discovers claims that should not have been paid, and reports and repays them, then (depending on the timing involved) the whistleblower will likely not be able to proceed with a whistleblower (or "qui tam") lawsuit.
- If a provider knows that it should not have been paid for certain claims, or if the provider "buries its head in the sand" and does not exercise "reasonable diligence" to determine if some claims should not have been paid, then the provider is racking up potential liability under the False Claims Act (FCA). Note that under the FCA, the provider can be liable for actual damages, treble damages, and up to $11,000 per claim.
- And so all of this boils down to the fact that the pharmacy needs to have a robust compliance program, conduct internal audits, and have an outside auditor come in periodically to conduct audits. When I say "robust compliance program," this means that the pharmacy should examine its document retention, examine how claims are submitted, determine if any of its operations violate the anti-fraud laws referenced previously, and provide regular training to employees.

Attribution: A portion of this article is attributed to two articles written by Jeff Overlay, senior reporter for Law360, on Feb. 11, 2016, entitled "Medicare Eases 60-Day Overpayment Rule" and "6 Policies in Medicare's 60-Day Overpayment Rule." ■

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Live Oak Bank: lending a helping hand to independent community pharmacies

by Josef Aukee

In the past six years, Live Oak Bank has helped community pharmacists start, build, or expand their businesses with more than 600 loans totaling $650 million. Meanwhile, the industry evolved, health care plans and providers saw radical change, and the technology revolution arrived for pharmacies. With challenges facing the transition of legacy pharmacies (such as predatory chains and reduced reimbursements), Live Oak brought a laser focus to pharmacy lending. It has a dedicated a team of seasoned experts in the field to help facilitate the transfer of ownership to a new generation of pharmacists with an entrepreneurial spirit.

This profile of the bank's early assumptions and objectives offers a close-up view of how pharmacy business financing has grown, the influence of industry changes, and practical tips for taking advantage of all that Live Oak offers.

HOW IT ALL STARTED

With a strong national footprint in small business loans for startups in industries as disparate as dental and veterinary practices, a few like-minded professionals met in the hallway at an NCPA conference in 2009. The organization would later officially partner with Live Oak to facilitate the financing of independent community pharmacies. Existing and prospective owners

soon began to apply for the funding required to refinance, expand, or acquire pharmacies.

This new partnership and a growing awareness of the bank's capabilities created a link to thousands of pharmacy owners and allowed prospective buyers to flourish. Many would-be owners were often turned away by traditional lending institutions, which treated community pharmacies much as they would any other small business, either rejecting proposals or offering financial terms that were impractical for the industry and prospective owners. By contrast, the Live Oak team, experts in both pharmacy and Small Business Administration (SBA) loans, understood and recognized the earning potential of community pharmacies and the value of resalable inventory and prescription files.

> ***In the past six years, Live Oak Bank has helped community pharmacists start, build or expand their businesses with more than 600 loans totaling $650 million.***

Commenting at the time, NCPA CEO B. Douglas Hoey, Pharmacist, MBA, said, "Independent community pharmacies focus on patient care and a wide array of services that their competitors cannot replicate, but it can be difficult for prospective owners to secure financing for these purchases. That's why this partnership between NCPA and Live Oak Bank is a game

Q & A With B. Douglas Hoey, Pharmacist, MBA, NCPA CEO

Can you comment on the importance of financing for independent community pharmacies?

"The 600 pharmacy loans over the last six years speak volumes. These are pharmacies that are still independent in no small part because of the loans available through Live Oak Bank. My guess is that at least half of those independent pharmacies would have been lost to one of the mega-chains if loans weren't available through LOB."

What community pharmacy financing needs do you see for continued success?

"Pharmacy margins are as tight as they have ever been, so having access to financing and capital is essential. Statistically, some pharmacy owners are nearing a time when they are considering retirement and looking to transition their stores to another independent. Financing will be available for the new owners of those stores. Also, every owner we talk to who has invested capital in their store to spruce up or remodel their stores has said the same thing: 'I wish I had done this sooner!' because of the boost in business and attitude resulting from the remodel. For major remodels, some owners seek financing to free up capital and cash flow."

How has a financing partner like Live Oak Bank changed the landscape over the past six years?

"For years, I looked for a lending source for independents that valued the 'blue sky.' I talked with big, medium, and small lenders. No dice. There were plenty of asset-based lenders, but most of them tried to value pharmacy inventory like it was a clothing store—very different! Live Oak filled a gaping hole that existed in the marketplace and hundreds of pharmacy owners, hundreds of independent pharmacies, and millions of patients patronizing those pharmacies are better for it."

changer. NCPA will use the full weight of its assets to alert potential buyers of this great lending resource."

While the size of this explosive market is difficult to determine, doing the simple math of a generational change in a health care sector supporting some 22,000 pharmacies means that more than 1,000 such legacy pharmacies change hands each year. Live Oak's first customers were often those needing refinancing of current loans, but the bank quickly moved into acquisitions, working capital for growth, expansion into compounding labs, specialty pharmacy and LTC facilities, and equipment and file buys.

"No one else has dedicated as many resources to pharmacy as Live Oak with 19 people on our team to provide the highest level of service," says Jimmy Neil, Live Oak general manager.

HOW CAN YOU PREPARE?

If you want to own a pharmacy and/or expand your business, you'll need good to excellent credit, and be prepared to contribute the most uncomfortable amount of cash you can toward the acquisition (typically 10 percent). You'll also want to be ready to convince an expert team that you have the skills necessary to accomplish your goals.

"We are looking for individuals who have a passion for succeeding," Neil says, "and have the ability to manage and operate a small business in a very challenging environment."

WHERE TO START

While some prospective entrepreneurs have connections to a legacy pharmacy, others have to do their research identifying potential opportunities in desired locations. While there are a handful of business brokers who specialize in pharmacy, most drug wholesalers have sales forces that manage specific territories and have a steady pulse on opportunities in a given local market. Wholesalers have a vested interest in keeping community pharmacies independent. NCPA offers an independent pharmacy matching service (www.pharmacymatching.com) devoted to bringing buyers and sellers together. Also, consider attending NCPA's Ownership Workshop sponsored by McKesson, a continuing education program

Q & A Success Stories: How Live Oak Bank Works for You

Saleem Shah
Patterson Park Pharmacy
Baltimore, Md.

Buoyed by a strong background in retail pharmacy at major chain pharmacies, Saleem Shah was ready to focus on his own business in specialty pharmacy in 2010. As an NCPA member, Shah made a connection with Jimmy Neil, who was working in pharmacy transition services for a major distributor at the time, and attended his first NCPA Ownership Workshop to explore options for acquiring an existing pharmacy. At the event, Shah connected with Live Oak's general manager just as it had launched its financing program for independent pharmacies.

Shah found a 100-year-old 2,000-square-foot pharmacy, secured the majority of the financing through Live Oak Bank, and set about transforming the business. Focused on specialty compounding as a plan to improve the business, Shah used much of the previous retail space for a compounding lab and proceeded to grow 1,700 percent over the next six years.

"The process was helpful every step of the way. Live Oak's staff had a real sense of ownership interest and helped with looking for possible deals, analyzing the current business, and looking at practical niches for the market," Shah says. "I think we closed the deal in a matter of months."

Using both reserves and an additional loan from Live Oak, Shah redesigned and built a more sophisticated lab to accommodate growth.

"Staying only in retail could have put me out of business. Today, owners must deal with a multi-faceted approach as the pharmacy industry is evolving, and with these changes, a more sophisticated operational approach should be adopted," Shah says. "You must change with the business."

Several factors are driving the changes, including a balance of power shift due to the effects of the Affordable Care Act and negotiating competitive rates. The pharmacy now provides specialty drugs for hormone replacement, HIV, complex wound care, pain management, and veterinary medicine. The pharmacy also uses proprietary software built on Shah's ideas and vision.

Shah is looking to the future, with growth areas such as the pediatric population with needs for autism and mental care solutions.

"Maintaining a relationship with Live Oak Bank is important as I look toward expansion and know that I have that leverage in my back pocket when opportunities arise," he says.

designed to help a prospective buyer become a successful independent community pharmacy owner.

Networking is essential. Use tools readily available such as local business groups, trade conferences, social media platforms such as LinkedIn, and community health care connections. Live Oak has found that the average age of pharmacy owners is 62, and recommends using a low-key confidential approach to connect with existing legacy businesses. Many traditional pharmacy owners are interested in a dedicated new generation of pharmacists who are committed to maintaining an established business with close ties to both employees and patients in a community.

Recent trends indicate high interest not only in acquisitions, but also in demand for expansion through long-term care facilities, specialty drugs (such as HIV, Hep C, fertility and others), compounding labs, and other high touch, patient-centered care services and automation.

"The winning characteristics we find in those seeking financing are often similar: those who are knowledgeable in pharmacy combined with a passion for caring for patients, a people-centered approach to innovation, a sense of customer service, and reliance on training staff to reflect their philosophy," Neil says. "These are people who take the time to know their patients by name and are engaged in the community where they live and work."

HOW FINANCING CAN HELP A STRUGGLING PHARMACY

Lower reimbursements from health care plans, PBM requirements, bottom line costs and the like are just a few challenges facing community pharmacy. In many cases, a willingness to innovate can address these issues. New technologies can help reduce staff time required to accomplish routine tasks, increase patient adherence to regimes, process claims, and automate communications with patients, providers, and suppliers. Embracing change has been the leading trend in the most successful pharmacies.

In the past, only 20 percent of disbursements were generics, but now as many as 90 percent of prescriptions are filled via that route. Community pharmacists have found ways to innovate by developing front-end

Q & A Success Stories: How Live Oak Bank Works for You

David and Kelly Dokimos
Dokimos' Pharmacy
Grass Valley and Nevada City, Calif.

David Dokimos landed in pharmacy in a traditional way. His father owned a community pharmacy which he worked in as a youth. After that pharmacy was sold, Dokimos attended pharmacy school and worked for a major chain for 21 years. Using a combination of self-funding and a local bank, Dokimos and wife Kelly opened their first pharmacy in Grass Valley, Calif., in 2004. Similarly, they expanded to a second location in Nevada City in 2007. In 2010, the couple wanted to refinance a myriad of loans and to secure working capital and additional cash flow.

"In a growing business, cash flow suffers whenever we must pay in advance, and there is a lag in accounts receivable from insurance carriers," Dokimos says. "Plus, we face challenges from big-box stores, third-party reimbursements, and participation in preferred networks."

When the Dokimos Family sought financing from a local bank, they found that there was minimal experience or understanding of the pharmacy business. That is when they discovered Live Oak Bank, which showed they understood the business, trends, and opportunities.

"Live Oak could look at the global picture of both of our stores and see our potential for success," Dokimos says. "The information that was required made sense and the Live Oak staff provided easy-to-understand explanations and did everything possible to make our financing work."

Regarding changes over the past six years, the Dokimoses pointed to the new challenges they face, including lower reimbursements, maximums for generics, Medicare Part D network participation, and changes to copayment amounts. To compensate for these obstacles, differentiators became more important. They concentrated on customer service, providing a positive experience, delivery, accommodating special orders, and expanding their retail mix to include front-end gifts.

"Live Oak Bank is the first place to go because of their expertise," Dokimos says. "They can help someone build from the ground up, including looking at real costs, identifying needs for financing and understanding the time it can take to build a customer base." The Dokimoses will look to Live Oak when they seek financing for purchasing a building.

Q & A Success Stories: How Live Oak Bank Works for You

Tom and Frances Lovett
Nambe Drugs
Los Alamos and Santa Fe, N.M.

With 43 years in the pharmacy industry, pharmacists Tom and Frances Lovett have seen many changes during their professional careers. These include owning their first pharmacy in the late 1970s and working with Sun Healthcare Group, Inc., as employees supporting U.S. and international pharmacies in the long-term care and hospital sectors. In the early 2000s, the Lovetts got back into the retail pharmacy business in New Mexico, and in 2010 established Nambe Drugs and a second store in 2015.

"We put together a prospectus proforma and went to meet with local banks, and no one was interested," Tom says.

At a business conference organized by a major pharmaceutical wholesaler, they met Jimmy Neil, who introduced them to Live Oak.

"They already knew the pharmacy business, and that congruency with our knowledge helped us," Tom says. "With Frances' work and training as a pharmacist clinician provider with prescriptive authority in an internal medicine medical office, we knew we needed someone who understood what patient-centered care meant."

As true patient advocates, Nambe Drugs moved into compounding and specialty drug care.

"It's like gourmet cooking with medication," Frances says. "It allows you to spend time with patients and solve troubling problems with unique insight to the body, disease and medication alternatives available, and that's when they become lifelong customers."

The pharmacy offers precise, pharmaceutically elegant medication solutions that require keen attention to detail at all levels of interaction.

"No doubt, we are specialists and love the art and science of independent pharmacy," Frances says. To manage the investments required to provide a high-level of service, Live Oak became an invaluable partner who understood that a credit line could allow the Lovetts to expand their personalized service and immunization services and reach the hospice and senior care facility sector.

"The personalized service from Live Oak is very different from other lenders in that it offers a face to the business," Tom says. "We were able to use financing for advertising campaigns to expand our service area, which resulted in the addition of a second store. I can't reiterate how critical their advice is to our success."

The Lovetts also noted that the process for applying for funds with Live Oak was easy and streamlined, with one key account person handling their case so that they could focus on keeping their business running.

"With an ever-changing world in pharmacy and no luxury to remain stagnant, a partnership with those such as Live Oak Bank is critical to success," Tom says. "Even the gift of the book, 'The Giving Tree,' we received from our Live Oak partners said it all — 'we're here to provide advice for life.'"

merchandise offerings, providing medication synchronization and delivery services, offering vaccinations, compounding, and specialty drugs, along with servicing LTC facilities.

Many of these services require investment that can pay dividends for years to come, not only through customer loyalty, but also by expanding the services that attract and maintain new patients and provider referrals.

WHAT THE FUTURE HOLDS

Live Oak Bank sees a bright future for community pharmacy. A team of industry experts in both pharmacy and financing can help bring businesses into the competitive landscape, rewarding those dedicated to patient care in ways that chains can never replicate. It has invested in programs with organizations such as NCPA to bring awareness to owners that tapping the resources required to meet new challenges is available for those pursuing success.

Neil says, "A strong track record needs no defense. We are confident in the future of pharmacy and are fully committed to helping both those businesses in transition and those stepping up to meet the challenges and opportunities for tomorrow." ■

Josef Aukee is a writer and marketing communications consultant based in Sausalito, Calif. His work covers a variety of business, events, health care, technology, and travel topics.

Care Transitions: *The Employer Perspective*

Payers are looking to information technology tools to rein in health care costs

by Bill G. Felkey

Employer health benefit managers increasingly want to hear about technology and how it can to help them achieve their goals. For years, I have known that information technology is a common denominator in all health care disciplines and specialties. I recently returned from a business coalition meeting where I spoke in a special session with a pharmacist who was offering consultation services on contracting with and auditing pharmacy benefit managers. Though I have been invited to speak with attorneys who focus on health care, most of my perspectives focus on the health care provider mindset with pharmacists, physicians, hospital CEOs and their boards, nurses and nursing executives, and physician assistants.

There is a changing employer perspective that we need to consider. Why? Because these employers, like the government, are the ones paying all the bills and trying to figure out how to control their health care expenditures. For example, every automobile manufactured in the United States has between $800 and $1,500 in health care costs associated with each vehicle that comes off the line. The United Auto Workers (UAW) is actively negotiating with the automobile industry, which is carrying $2 billion in health care fees for 135,000 employees and their families. Business coalition leaders are saying that health care suppliers keep raising their prices, and businesses just keep paying those prices. They are trying to figure out how they can slow this progression.

SHIFTS IN COVERAGE

How familiar are you with acronyms such as HDHP, HAS, and HRA? You live this every day, but I was surprised to learn from a national business coalition leader that 83 percent of all employers are now offering high-deductible health plans (HDHP) to their employees, up from 67 percent last year. Employee-owned health savings accounts (HSA) are now being used by 56 percent of U.S. business owners. And 18 percent of employers are setting up health reimbursement accounts (HRA). From a motivational perspective, this move means working with patients to make lifestyle changes, which can give them immediate monetary benefits. Becoming adherent to their medications and avoiding hospitalization brings about new opportunities to get patients' attention and help them manage their care transitions. You might be interested to know that specialty pharmacy was targeted as the latest out-of-control expense item.

So, what are employers seeking from health care providers? They are looking to form partnerships and gain advocacy relationships, replacing their health benefits with something they describe as the "employee experience." They have to recruit the best workforce for success, but the experience that workers have, including their health care, is what retains and promotes necessary innovation to change and stay

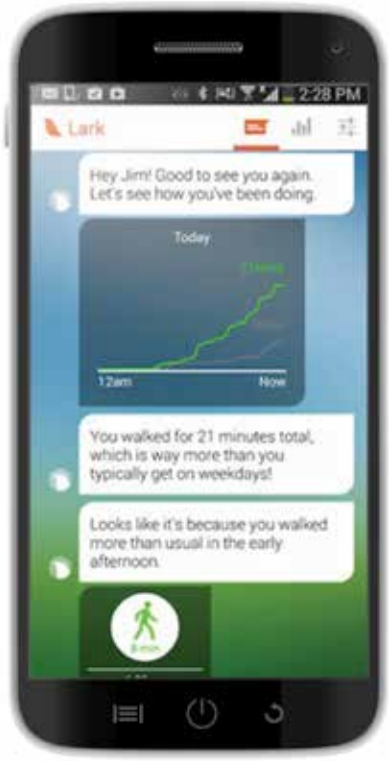


Figure 1. LARK is a free health coach app that can aid patients in the lifestyle changes mandated during transitions of care. It provides information, encouragement and logs activities, meals and outcomes data in a single place.

successful. A lot of what they see in technology includes using telehealth channels for their workforce. An organization called Doctors on Demand facilitates virtual visits and second opinions via smartphone. Do your local businesses know that a prescription can be delivered to the workplace to an employee who can stay on the job if that worker's non-infectious symptoms are relieved?

EMERGING TOOLS

Tools are emerging to assist in the well-being and preventative lifestyle changes that so many workers need. For example, I have been using a free health coach app called LARK. (See Figure 1.) It reminds me to log my meals and then rates them as being healthy, neutral, or unhealthy. It tracks my activity (automatically or by data entry) and connects to my blood glucose meter and the health app on my phone, which then connects to my digital scale and Bluetooth blood pressure cuff. As I am sitting here writing, my LARK app chimed and said, "I am saying this in love Bill, but I noticed that you have not moved in over two hours. What would you think about getting up and taking a short walk right now?" As for results, I have lost 26 pounds in the last 90 days. As one of my friends said, he knew he needed to do something when he got a shoeshine and had to take the guy's word for it.

The concept of OnSite/Near Site is another potentially effective method to produce that employee experience. When was the last time you went to a workplace and provided a health

Figure 2. PatientsLikeMe is a trusted health website that provides expert advice and allows for patients to share and connect with other people who are coping with the same health challenges they are.

screening, flu shots, or other health positive efforts that would be embraced by both employers and employees? Employers also believe that social networks and trusted health care websites are an important piece of the puzzle for controlling their overall costs. They do have concern about going too deeply into patient information areas. You are probably aware that patients fear their jobs will be terminated if they represent a large drain of health care dollars spent. You can serve as an intermediary who protects patient confidentiality by reporting group achievements for your partnering efforts.

GUIDANCE FOR PATIENTS

In my presentations, I a pass out a homework assignment instructing every meeting participant to go to www.PatientsLikeMe.com and observe how patients who have been diagnosed in a primary care environment are being helped. Some of these are patients have been dispensed prescription drugs from a pharmacy, creating new medication regimens that are unfamiliar to patients. Others have been discharged from an acute care setting and need to transition from that environment to self-care management. (See Figure 2.) Both scenarios can provide challenges for patients. The website addresses the reasons why patients typically fail in their self-care management: they don't know what to do, they don't know how to do it, and most difficult of all, they may not be motivated to make the changes necessary to achieve their best possible health status.

PatientsLikeMe allows patients to get useful information from experts. These experts also receive feedback about the advice they offered, with suggestions on how they might tweak/enhance the process to provide even better results for those seeking answers. For example, links to textual information can reduce uncertainty, but links to video resources can show people how to actually do the behavior they are being asked to model. And perhaps most importantly, patients who

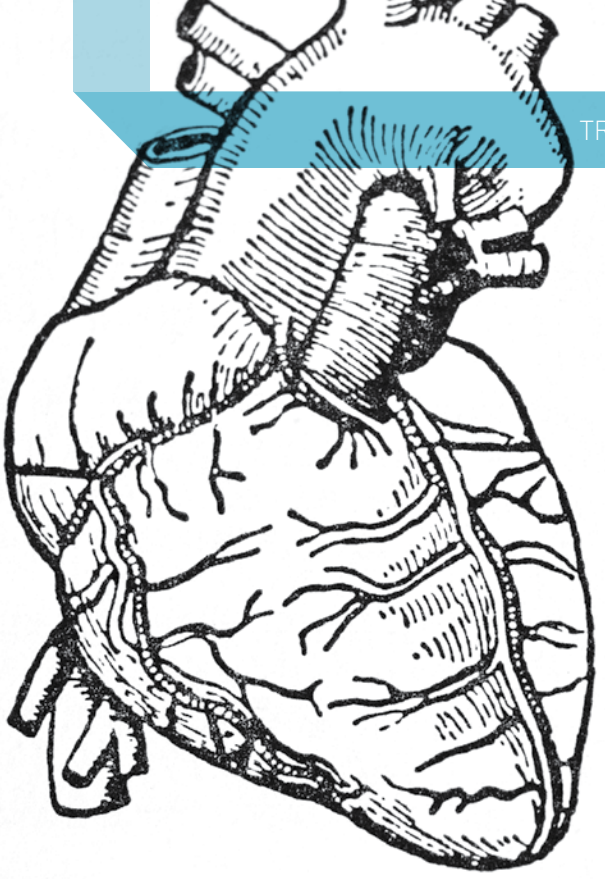
have been newly diagnosed with a condition can partner up with other patients with the same or similar condition and get help, encouragement, and motivation to do the needed lifestyle changes, and then continue with these changes over time until they become a life benefiting habit. This website doesn't cover every condition, but you will see how to emulate what they do, and you can tailor an effort on the different diseases needed by your patients using their approach.

WHAT'S ON THE MINDS OF EMPLOYERS?

There are two other areas that impact you that are on the minds of employers. First, they believe health care needs someone to act as a concierge for their workforce. Can you see yourself, given the access that patients have to you, as somebody who can serve as a patient care coordinator? The internet is full of information about what patients at different ages need for their health at any given point in life. This is something health care benefit managers can hear from you, but they would also need to know that you are helping patients in this capacity. The second area involves the movement toward population health, where accountable care organizations (usually health systems) will sign on with employers to manage the health care of their entire workforce. ACOs will receive health care dollars (in some cases, directly from employers) without the need for insurance agencies to rake off administrative fees before any health care provider is reimbursed. In this scenario, every transition of care will come under the scrutiny of a provider network who is totally at risk for that population's health.

For employers to focus on success in their businesses, they need to control the dollar spend for their health care benefits. For an integrated provider network to be successful, it needs to be tightly affiliated or wholly own every part of the care continuum. In this environment, it would benefit you if both employers and health systems were aware of your interest in participating in these changing environments. If you have questions or comments, and especially if you are seeing your practice being impacted by these changes already, please feel free to contact me. I can be reached by email at felkebg@auburn.edu. Let me know how I can help. ■

Bill G. Felkey is professor emeritus at Auburn University's Harrison School of Pharmacy.



Pharmacists Can Help Reduce Acute Myocardial Infarction Readmission Rates

by Mary Rothermal, PharmD

BACKGROUND

As stipulated by the Affordable Care Act, hospital reimbursement is now a reflection of a facility's 30-day readmission rates of specific disease states, including acute myocardial infarction (AMI). Rising health care costs and suboptimal patient outcomes resulted in an overhaul of the Medicare reimbursement model. According to data from the Centers for Medicare & Medicaid Services (CMS), AMI is both one of the most expensive conditions to treat and associated with one of the highest readmission rates. The Agency for Healthcare Research and Quality (AHRQ) defines this readmission measure as an unplanned readmission, of any cause, to an acute care hospital within a 30-day window of time following discharge for AMI. In 2005, the Medicare Payment Advisory Commission (MedPAC) reported that 13.4 percent of AMI patients are readmitted within 15 days of discharge; this figure equates to an astonishing $136 million of hospital care. A number of these readmissions were due to avoidable causes such as failure to receive necessary medications, miscommunication between the provider and patient, lack of support at home, or poor access to follow-up care. Shared responsibility and fluid communication among all health care practitioners is necessary to assure complete continuity of care. Ensuring this continuation of care will directly improve the overall health of patients, especially those who recently suffered an AMI. The need for outpatient involvement in patient care has never been greater; pharmacists in the community setting can and will directly impact the readmission rates of nearby hospitals and, more importantly, will positively impact their patients' health.

Editor's Note: *For information on references used in this article, contact Chris Linville at chris.linville@ncpanet.org.*

HOW CAN PHARMACISTS HELP?

After a review of available literature, the Joint Commission identified and summarized the effective approaches to transitions of care. This compilation includes a number of processes that can be effectively performed by a pharmacist, such as identification of those at risk for readmission, medication reconciliation, and improved education to both patient and family. Given the known high readmission rate, any patient discharged after AMI will require extra attention for a successful transition. Upon discharge, AMI patients face a number of challenges, including a new diagnosis to accept, initiation of new medications, access to medications, adherence to their medications, and medication-related adverse effects. Pharmacists, especially community pharmacists, are in a unique position to assess the patient's situation, identify any gaps in care or communication, and then provide individualized care and ameliorate any medication-related issues to ensure a smoother transition post-discharge. Whether it is the standard of care for the pharmacy or part of a formal collaborative transition of care effort with the discharging facility, a pair of phone calls, one within 72 hours and the other at the two-week mark, can go a long way toward identifying medication issues that could lead to a readmission. A technician can ask three questions

and either get the pharmacist's attention immediately or record patient responses for pharmacist review.

SAMPLE QUESTIONS A TECHNICIAN MIGHT ASK

- How do you feel today?
- How is your mood/sleep/appetite/energy/motivation today? (depression screening)
- How do your (new) medications make you feel?
- How often are you going to cardiac rehab?
- How does cardiac rehab make you feel?
- When is your next doctor appointment? Do you need help getting there?

WHAT SHOULD PHARMACISTS FOCUS ON?

Adherence

The American College of Cardiology (ACC) reports that 31-58 percent of patients taking medications for cardiovascular disease are non-adherent to their medications. To illustrate the significant impact of that nonadherence, the ACC also reports that 33-69 percent of medication-related hospital readmissions are due to suboptimal adherence. Patients who recently suffered an AMI are likely to leave the hospital with a number of new medications, and adherence to those medications must be encouraged and their side effects monitored. Studies show that adherence is more difficult to achieve as the number of medications increases. From a number of sources, pharmacists can identity their patients who would benefit from an adherence check; sources include medication therapy management (MTM) platforms, pharmacy management software that calculates adherence rates, or from face-to-face conversations with their patients. Equipped with this information, community pharmacists can make interventions with their non-adherent patients and educate their patients beginning on new medications about the importance of being adherent. A useful tool available to community pharmacists is called the Drug Adherence Work-up Tool, commonly known as the "DRAW" tool, available through the Million Hearts "Team Up. Pressure Down." initiative (http://millionhearts.hhs.gov/docs/tupd/draw _ tool.pdf). This worksheet can help guide the pharmacist-led adherence intervention through the use of patient-directed, open-ended questions. The initial field test of the DRAW tool found that 77.3 percent of patients reported more than one reason for nonadherence. As a pharmacist, don't always accept, "I don't need any help with my medications" as a response, especially from your AMI patients. Even the most competent patients may benefit from post-discharge medication counseling and an adherence check. Future hospitalizations can be directly avoided if adherence to necessary cardiovascular medications is optimized.

MEDICATION THERAPY MANAGEMENT ENCOUNTERS

Without question, medication therapy management is one of the most valuable services offered by the community pharmacist. These services can take place in the comfort of the patient's pharmacy and by his/her pharmacist. During an MTM encounter, the pharmacist is able to optimize medication regimens, promote preventative and nonpharmacologic measures, identify and correct barriers to access or adherence, provide education, and use motivational interviewing skills. The significant impact pharmacists can have on readmission rates was illustrated in a study conducted at Group Health Cooperative in the state of Washington. Patients who received a medication reconciliation and assessment post discharge had decreased 30-day readmission rates as compared to those patients who did not have a pharmacist intervention.

MTM encounters can also provide a safe place for the patient to disclose gaps in their understanding of medications or their disease state(s). A study done by Attebring et al. revealed a large portion of AMI patients were confused about the cause of their AMI and the role of medication in their care. During an MTM appointment, pharmacists have the opportunity to identify and dissolve any misconceptions that may surround a patient's medications. Overall, MTM is the ultimate framework for pharmacists to educate AMI patients, counsel individually on their complete medication list, optimize medication regimens, and bill for pharmacy services.

CONCLUSION

Due to the complex medication regimens and probable medication-related adverse effects associated with post-AMI treatment, pharmacists are invaluable members of the interdisciplinary team caring for this patient population. The community pharmacist is key in promoting medication adherence, optimizing medication regimens, and patient education—all of which are imperative in preventing hospital readmission following an AMI. ■

Mary Rothermal, PharmD is a 2016 graduate from the University of Michigan and was a fall 2015 APPE Rotation Student at NCPA.

Editor's Note: *This is the first of a series of six articles that will be published in* America's Pharmacist *covering various health issues surrounding transitions of care when patients are discharged from hospitals, and how community pharmacists can help ease the transition and play a key role in avoiding costly readmissions to hospitals. Access NCPA's Transitions of Care toolkit at www.ncpanet.org/toc.*

Planting the **Ownership Seed** with an *Entrepreneurship* Elective

University of Arkansas wins Student Business Plan Competition

by Chris Linville

A shared passion for the entrepreneurial side of pharmacy and a legacy of past success help bring four students from the University of Arkansas for Medical Sciences College of Pharmacy together to compete in the 12th annual 2015 Good Neighbor Pharmacy NCPA Pruitt-Schutte Student Business Plan Competition, held last October at the NCPA 2015 Annual Convention in National Harbor, Md., just outside of Washington, D.C.

Team members Luke Morrison, Christina Watkins, Kristen Belew, and Brooklyn Pruett, all May 2016 PharmD graduates, were drawn to pharmacy in varying ways before bonding together for success.

Morrison says, "I became interested in pharmacy after hearing a pharmacist speak in a medical professions elective in high school, and also after shadowing a pharmacist from my church."

Watkins says her high school chemistry teacher introduced her to the profession. "She brought in speakers from the UAMS College of Pharmacy and did a great job of sharing aspects of the profession throughout the school year," she says.

Belew says her interest in chemistry helped push her toward pharmacy. "It developed in high school with a creative teacher, which then turned into a college major where I met more caring professors," she says. "With their guidance, I applied to pharmacy school, as it was an opportunity to further my chemistry interest but serve other people. I am very thankful for the teachers and professors that have influenced my career for the better."

Pruett says she learned about pharmacy after shadowing a good friend's mother, who is a pharmacist in her hometown. "I had always been interested in science and math in high school, and I wanted a career that was different and challenging every day," she says. "Pharmacy is the perfect mix of sciences, a challenge, and patient interaction."

Rhea Specialty Drug, LLC was the winning proposal from (L-R) Cristina Watkins, Luke Morrison, Kristen Belew, and Brooklyn Pruett.

The 2014 UAMS team knocked on the door, finishing third in the business plan competition, and the school has consistently has had a number of top 10 finishes in the event over the years, so the 2015 team had extra motivation to continue the tradition.

"UAMS has a well-established legacy of teams that have scored well in the Pruitt-Schutte competition," Belew says. "I watched every business plan team present during my first, second, and third year of pharmacy school. I was impressed with their creativity and business tactics."

And in 2015, the judges were equally impressed with UAMS's tactics, as it was named the winner of the event. Its proposed business was Rhea Drug, LLC, a specialty pharmacy based in Little Rock, Ark.

The first national competition of its kind in the pharmacy profession, the Pruitt-Schutte Student Business Plan Competition was created in 2004 and was named in honor of two champions of independent community pharmacy, the late Neil Pruitt Sr., and the late H. Joseph Schutte. The competition's goal is to motivate pharmacy students to create a business model for buying an existing independent community pharmacy or developing a new pharmacy.

UAMS's team advisors were Dr. Seth Heldenbrand and Dr. Schwanda Flowers, along with the school's dean, Dr. Keith Olsen. Their NCPA chapter received $3,000, and $3,000 was contributed to the school in the dean's name to promote independent community pharmacy. The team members, team advisor, and the dean also received complimentary registration, travel, and lodging to NCPA's 2016 Multiple Locations Conference in February in Fort Myers, Fla.

The two other 2015 finalists were a team from the South Carolina College of Pharmacy (second place), and another from the University of Minnesota College of Pharmacy.

In the following interview, the team members discussed how their plan for Rhea Drug, LLC, came together, what they learned about the business of pharmacy, and what pharmacy ownership means to them.

WHY DID YOU DECIDE TO ENTER THE PRUITT-SCHUTTE COMPETITION?

Luke: I enrolled in an entrepreneurship elective where I knew the competition would be the focus of the semester. I wanted to take the class and compete because I desired to learn as much as possible about ownership and pharmacy business. It is a dream of mine to own pharmacies in the future.

Christina: The college offers an entrepreneurship class as part of the elective curriculum. Before coming to pharmacy school I had earned a BBA in finance, so the business aspect of pharmacy really piqued my interest. Also, as a P1 and P2, I watched the UAMS business plan teams make presentations, and knew I would enjoy being a part of the team.

Brooklyn: As a P1, I remember watching the UAMS business plan team present at our local student NCPA meeting. The presentation was amazing and the business idea was genius. I knew then that I wanted to try to compete in the competition. I enrolled in the entrepreneurship class and was lucky enough to be put on a team with friends. We each have a competitive spirit and from the beginning we knew we wanted to make it to Washington, D.C. (by finishing in the top three).

HOW DID YOUR TEAM COME TOGETHER?

Luke: Our team came together on the first day of the entrepreneurship class. Our professor told us at the end of the lecture to divide into teams on our own and to be ready to present potential pharmacy ideas by the next class period.

2016 Business Plan Live Competition Set for Oct. 15

To see more inspiring future pharmacy owners and and hear their innovative ideas, join us at the 13th annual 2015 Good Neighbor Pharmacy NCPA Pruitt-Schutte Student Business Plan Competition on Saturday, Oct. 15, at the NCPA Annual Convention in New Orleans. The three finalists will present their winning pharmacy concepts and strategies for success. Find out more about attending the convention at www.ncpanet.org/convention.

We decided on one another as teammates because we all really liked each other.

Christina: We were told that preparing the business plan would require a lot of time and effort outside of class time. Therefore, students who were friends outside of class and spent time together outside of class generally formed the most successful teams. This was an easy decision for our team as two of my close friends, Brooklyn and Kristen, were also in the class. Luke was an excellent fit as well.

Kristen: When it was time to select our groups, Dr. Flowers suggested that we select business partners that will work well together. Thankfully, two of my best friends, Brooklyn and Christina, were in the class along with Luke, who had a reputation of being a hard worker. It was a perfect dynamic as we solved problems together and encouraged each other.

Brooklyn: We each entered in the entrepreneurship elective offered at our school. The class teaches different aspects of owning a business and the main project is to create a business plan. It worked out really well because we were all friends before the class and when the professor said we could pick our own teammates, we knew we wanted to work together! Working together was easy and we found ourselves talking about the business plan even when we were just hanging out.

WHEN DID THE GROUP START DEVELOPING THE BUSINESS PLAN?

Christina: We started developing the business plan in January of 2015. We turned in our written plan toward the end of the semester and then prepared to present it to classmates, faculty, and local pharmacy entrepreneurs in hopes of securing the prize of claiming the submission to the national competition.

Kristen: We spent the first two months brainstorming ideas and meeting with a variety of pharmacists. Creating the idea was the hardest part. Once we settled on the main idea of creating a specialty pharmacy, the plan developed at a rapid speed.

Brooklyn: We worked all semester during the entrepreneurship elective to create our plan. At the end of the semester we presented to compete with others in the entrepreneurship class. We were thrilled when our plan was chosen to submit to NCPA in May 2015.

HOW WAS THE PLAN FORMULATED? WHO CAME UP WITH THE IDEA?

Luke: We knew we wanted to buy out an existing pharmacy as opposed to doing a startup business. Kristen was a pharmacy intern at a local independent pharmacy that had an interesting patient niche. We all decided our best option was to open a specialty pharmacy within the existing store and also to update several aspects of the retail business as well.

Kristen: If we could buy an existing store, our business plan would appear more successful or realistic. I worked at an independent pharmacy that already had a niche with HIV patients. In the 1980s, an HIV shelter opened in a nearby neighborhood, and Rhea Drug filled all supportive medications. Rhea Drug remained the word of mouth recommendation for HIV patients for decades to come. HIV support was a real need of this community, and we wanted to improve the service they were receiving.

Brooklyn: On the first day of class we started brainstorming ideas. We knew we wanted to "buy" an existing pharmacy and make changes to better serve the patients and increase profits. Many of our patients had specialty pharmaceutical needs and we knew a specialty pharmacy would better serve them. We started researching specialty pharmacies and ran with that idea.

HOW DID THE PLAN EVOLVE? WHAT WERE THE KEY STEPS YOU TOOK?

Kristen: In January, we started to brainstorm ideas that served a unique need of the community. We met with a variety of pharmacists and researched pharmacy business. In March, we started to write the content of our business proposal, and evenly split up the work among us. In April, we worked on the appearance and visual graphics of the proposal before sending in the 70-page PDF for the competition. We were named to the top three in July, and quickly started to prepare for the oral presentation. The PowerPoint presentation required thoughtful creation so that we could visualize our professional yet innovative ideas. We met twice a week to present to college faculty, students, family, and pharmacists, and always welcomed constructive criticism. When we presented in Washington, D.C. at the NCPA Convention, we could say those lines in our sleep. We were very proud of our performance, and thankful to see all of the hard work come to completion!

Luke: The written plan evolved over four and a half months from January to May of 2015. I was responsible for the specialty pharmacy portion of the plan as well as corporate structure.

WHAT WERE THE MOST IMPORTANT THINGS TO ADDRESS EARLY? WHAT CAME LATER?

Luke: The first things we addressed were who was responsible for different portions of the plan. We felt it worked best to divide and conquer. We would then discuss and give feedback on one another's work.

Brooklyn: I think the most important thing we did in the beginning was dividing up different parts of the plan for each person to work on. Someone was in charge of location analysis, marketing, the specialty pharmacy, the retail pharmacy, the front end, and other details. We each worked on our assigned parts for the rough draft. When

it came time to edit the plan we all sat down together and went through each part, changing things as a group.

Kristen: Dr. Flowers always pestered us with the question, "How will you get paid?" She strongly recommended that every service offered came with a reimbursement. We first researched 340B pricing, but felt limited with the population requirements. Next, we started looking into buying groups for specialty pharmacy, and realized their buying power for HIV drugs.

WHAT WOULD YOU CONSIDER TO BE THE BIGGEST HURDLES OR CHALLENGES?

Luke: The biggest challenge for our business model was going to be getting the specialty pharmacy in network with third parties and their PBMs. We provided financial predictions conservatively knowing that we would not be able to obtain every single customer.

Brooklyn: There were many unknowns, especially with a specialty pharmacy. We had to do a lot of research about specialty pharmacy, regulations, and accreditation. I think that was the hardest part because none of us had ever worked in a specialty pharmacy. We wanted this plan to be as real as possible.

WHAT WOULD YOU CONSIDER TO BE THE BIGGEST FAVORABLE FACTORS?

Luke: We improved the pharmacy in many ways that would significantly improve the bottom line. Instead of buying specialty medications in the typical manner, we chose a specialty specific group purchasing organization that happened to be in network with our wholesaler for a generous discount. We also increased profitability on the retail side of the business by re-focusing our purchases with one wholesaler, installing a drive-thru, offering immunizations, and much more.

Christina: I believe acquiring accreditation and gaining access to specialty GPOs are the biggest factors in the success of the specialty pharmacy. These factors alone allow us to increase our profits on HIV medications even before the pharmacy acquires a single new patient, solidifying the success of the specialty pharmacy.

> ***This process helped me to learn a lot about starting a business and also allowed me to network with many pharmacy owners. After the experience, I am really encouraged to open a store.***

Kristen: Rhea Drug already had a target market and was proven successful in the community. Our plan would only enhance its niche while adding pharmacy services.

WERE THERE ANY MAJOR THINGS THAT SURPRISED YOU?

Luke: It surprised me at how well our group worked together. Our advisors [Heldenbrand and Flowers] also meshed really well with the team. We all made the plan its best by contributing with our different strengths.

Brooklyn: I was surprised with the amount of people in the community that wanted to help us, even though this was a school project. Our professors put in so much time outside of the classroom to help us succeed. Pharmacy owners around the community were also very gracious. Each of them were always there to answer questions and offer up information to help us learn and make our plan better.

IN TERMS OF FINANCES, WHAT FACTORS CAME INTO PLAY?

Kristen: We used a few raw numbers from the existing pharmacy, such as gross sales, cost of goods sold, average daily script count, and rent. We then extrapolated numbers based on the *NCPA Digest* sponsored by Cardinal Health for independent pharmacy owners.

Brooklyn: Christina and I tackled the finances for our plan. We used the *NCPA Digest* to try to keep our numbers as realistic as possible.

WHAT DID YOU LEARN THE MOST FROM THIS PROCESS?

Luke: This process helped me to learn a lot about starting a business and also allowed me to network with many pharmacy owners. After the experience, I am really encouraged to open a store.

Kristen: This project reassured my belief in the old saying, "you get out what you put in." After 10 months of vigorous preparation, I was incredibly proud of our business plan. I can absolutely see how this is true of business owners too. When you dedicate your life to doing good business, you find satisfaction in creating a safe business culture and serving others.

Brooklyn: The business plan was a lot of hard work and a year of growth for me personally. I am grateful for the knowledge I gained toward the business side of pharmacy and pharmacy ownership. We learned a side of pharmacy that is not normally taught in pharmacy school.

WHAT ADVICE WOULD YOU GIVE TO OTHERS?

Luke: The only advice I can give is to go for it. If you are willing to venture outside of your comfort zone and commit yourself to the work, the learning experience and the benefits you will receive are immeasurable.

Christina: The business plan competition was definitely the highlight of my pharmacy school career. It requires a tremendous about of time and effort, but the learning experiences, networking opportunities, and other benefits are absolutely worth the sacrifice. I would suggest that students decide from the beginning to be committed to winning and to form a team with others who share their passion. Be innovative and creative in your written plan as well as the presentation and believe in what you are presenting. These things will set you apart from the competition.

Kristen: Take one step at a time. Creating a business plan can be extremely overwhelming, but with teamwork and persistence, anything can be accomplished.

Brooklyn: Pick your team wisely! You will be spending a lot of time with them. I think we were largely successful because of the great teamwork we had. Try to select team members that you get along with and will also carry their weight when it comes to putting in work for the plan. Our team worked great together and I think that showed in our final product. ■

Chris Linville is managing editor of *America's Pharmacist*.

Counseling Patients on the Use of Pharmacotherapy for Insomnia

by Nicole Van Hoey, PharmD

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Pharmacist Objectives
By completion of this program, pharmacists should be able to:

1. Distinguish signs and symptoms of insomnia disorder in the community setting.
2. Assess patient medical history and daily routine for medical/pharmacological or behavioral causes of insomnia.
3. Explain the pathophysiology of the sleep-wake cycle and of hormonal sleep controls as they relate to falling or staying asleep.
4. Select the appropriate OTC option for new-onset insomnia or determine when to refer patients for medical care.
5. Discuss the different practical administration benefits and risks associated with established and new prescription classes for insomnia.

Technician Objectives
By completion of this program, pharmacy technicians should be able to:

1. Distinguish signs and symptoms of insomnia in the community setting.
2. Identify patient behaviors, conditions, or medicines that may cause insomnia.
3. Explain how problems falling or staying asleep develop.
4. Select an appropriate OTC option for new-onset insomnia.
5. Discuss the benefits and risks associated with established and new prescription insomnia treatments.

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INTRODUCTION

Disturbed sleep may be one of the most common yet inadequately treated health conditions shared by people across the globe. Nearly 70 million people across the United States have a diagnosed sleep disorder, and approximately 50 percent of U.S. adults each year report having trouble sleeping. Insomnia can be defined simply as the inability to sleep, but many complexities hide in that definition. Sleeping difficulties affect people of all types and ages; they may be an acute reaction to an identifiable cause or can develop into a chronic concern that contributes to accumulated sleep debt—the difference between how much sleep is recommended and how much actually takes place. Personal and socioeconomic costs of insomnia develop from lost work productivity, accidents, and increased physician and pharmacy visits. Despite the clear adverse effects of poor sleep, the causes and progression of insomnia make it continually difficult to treat successfully.

CASE PRESENTATION

Patient A.H. has filled prescriptions (for diabetes and nasal allergies) at your pharmacy for the past four years. She is a 36-year-old mother of three kids younger than 6, and she is in today for an annual flu shot. She has a bottle of a common over-the-counter (OTC) sleep aid (which contains diphenhydramine and acetaminophen) in her cart.

WHAT IS INSOMNIA?

One of 10 sleep-wake disorders identified in the Diagnostic and Statistical Manual of Mental Disorders, insomnia disorder is defined broadly as a problem falling or staying asleep, and is specifically associated with a feeling of distressed or unrefreshed sleep that affects daytime function. Sometimes, insomnia develops without an identifiable cause, named primary insomnia. In secondary insomnia, a known condition triggers the sleep disturbance. Insomnia can be additionally characterized into acute and chronic subtypes.

Acute insomnia is also known as adjustment insomnia, because it frequently develops when a person is adjusting to a lifestyle change or stressor, such as anxiety about an illness or death, job change, or other type of loss. This common subtype rarely lasts more than 30 days and can resolve without treatment as the body's sleep-wake cycle and neurochemical balance resets itself. The annual U.S. prevalence of brief adjustment insomnia is approximately 30 percent.

When insomnia lasts for more than 30 days, especially if it begins to change daily actions, it becomes a chronic disorder. Chronic insomnia can develop subsequent to acute insomnia or, in more than 75 percent of occurrences, as a result of other physical or mental conditions. Of surveyed adults with insomnia, 10 percent reported chronic problems that occurred more than three times weekly or for more than three months. The chronic subtype warrants evaluation by a health professional to identify the potential conditions that, if treated, will resolve the sleep disorder.

The progression of acute insomnia beyond 30 days is known as psychophysiological chronic insomnia. Here, concern about the original stressors evolves into persistent acute anxiety about the ability to fall asleep. Many of these patients tend to underestimate the amount of sleep they actually receive each night.

Causes

Causes of chronic insomnia, when identifiable, fall into four categories: physical conditions, mental conditions, medications or supplements, and behavioral or lifestyle factors. Pain is a dominant physical contributor, most often as a result of arthritis, back pain, or cancer pain. Physical illnesses that change sleep schedules and increase stress also contribute. Mental disorders frequently coexist with insomnia too: approximately 80 percent of people with depression report insomnia, and approximately 40 percent of people with insomnia are diagnosed with a variety of concomitant mood disorders. Medications and supplements, and the timing of these products, can trigger sleep disturbances and poor sleep habits. For example, thyroid medications mimic endogenous thyroid hormones secreted during the sleep-wake cycle. With high doses, especially if taken later in the day, patients remain stimulated and awake into the evening hours. Caffeine and marketed stimulant products (including energy drinks) induce neuronal arousal over rest, as do illicit products such as amphetamines.

Lifestyle and behavioral choices are closely related to sleep habits but are less likely to be discussed in the pharmacy. However, these highly individualized habits can be key to understanding why insomnia occurs and how to effectively treat it. Evening stimulation, especially when associated with extra light sources such as electronic devices, alter the body's ability to release hormones that trigger sleep and can instead trigger the release of arousal hormones, such as cortisol. Even seemingly minor evening habits, including the timing of meals and exercise, can disrupt sleep.

Manifestations of Chronic Insomnia

As insomnia continues to be left untreated, the body's sleep debt accumulates and leads to symptoms that bring patients to the pharmacy. Common early adverse effects include mood changes like anger and tension; poor focus and attention; and memory difficulties. As insomnia continues, poor motor function, headache, stomach upset, inability to function at work or socially, and increasing accident rates develop. Patients with chronic insomnia lose nearly eight days of work each year, at a cost of $63 billion per year.

According to the Centers for Disease Control and Prevention, insomnia disorder is a public health concern not only because of its broad patient population, but also because of the serious societal risks that result from untreated insomnia—such as greater numbers of motor vehicle collisions and medication errors.

HOW DOES INSOMNIA OCCUR?

Insomnia develops in a variety of people in response to complex, individualized combinations of physical and psychological triggers; these triggers change the balance of neurochemicals and hormones in the sleep-wake cycle differently in every patient. One unifying but perhaps simplified concept is that of hyperarousal—the imbalance tips the patient's nervous system (both central and peripheral) into activation instead of quiet. These changes can be quantitatively measured by, for example, increased heart rate and electroencephalogram (EEG) changes in a sleep lab. Hyperarousal is felt by patients themselves, too, who might admit that they cannot stop their thoughts from racing.

Endogenous molecules with an array of primary functions can be grouped into wake-promoting or sleep-promoting classes. Sleep suppressors (wake promoters) include histamine and orexin. Sleep promoters include molecules commonly used to exogenously change sleep patterns: serotonin, melatonin, prostaglandins, and gamma-aminobutyric acid (GABA). GABA broadly inhibits neuronal activity, so it remains the main target of most prescription treatments. New research into the role of other molecules that may offer more specificity and fewer side effects is ongoing.

Along with neuronal molecules, hormones (such as cortisol, thyroid-stimulating hormone) from systems such as the adrenal and endocrine systems interact with the nervous system to affect the body's ability to be alert or at rest. In particular, the cortisol's role in insomnia is well studied. Cortisol's role in the hypothalamic-pituitary-adrenal (HPA) axis is integral to sleep routine, so any disruption to the regularity of cortisol levels can lead to insomnia. Cortisol levels are at their highest in the morning (around 9 a.m.), as melatonin is at its lowest. After about 2-3 hours of sleep, cortisol levels begin to increase slowly until their morning peak. Disruption of cortisol patterns can be a cause of insomnia or a response to anxiety about ongoing insomnia, because cortisol activates alertness and is released in stress responses. Exercise, caffeine, meals, medication timing, and combinations of these factors also can increase cortisol and reset its normal decline in the evening to delay sleep.

One sleep aspect pathophysiology that overlaps between insomnia and other sleep disorders is the circadian rhythm or cycle. This rhythm uses melatonin to guide the body into restfulness on a regular path. Melatonin is made in the pineal gland and is released every evening as a result of a hypothalamic trigger. Its release, which correlates directly with the absence of light, occurs around 9 p.m. naturally. Melatonin remains high for 12 full hours before it falls to a low of nearly zero by 9 a.m. Thus, melatonin naturally follows the cycle of light and dark in a 24-hour day. Melatonin release is diminished by excessive direct sunlight or bright artificial light. In patients with circadian rhythm disorder, a separate diagnosis from insomnia disorder, the patient's melatonin release and light-dark exposure are misaligned, and insomnia or other sleep disruptions result as a symptom. Exogenous melatonin products (both OTC and prescription) are available to treat circadian rhythm disorder and its associated sleep problems. Melatonin does not work as well in patients whose melatonin release is already aligned, though, and should be reserved specifically for patients whose sleep patterns do not follow usual daylight patterns (such as shift workers, cross-time-zone travelers).

Sleep disruption that patients may report as insomnia (the inability to fall or stay asleep) should be assessed not only for circadian rhythm disorder but also for other known sleep conditions. For example, sleep deprivation—the lack of enough sleep—also accumulates sleep debt like insomnia and may lead to poor sleep habits that later promote insomnia. However, sleep deprivation is distinct from insomnia disorder, because the lack of sleep results from the patient's choice to sleep too few hours.

What Are Appropriate Sleep Goals?

According to the National Institutes of Health and the National Sleep Foundation, most adults 18 and older should aim for 7-9 hours of sleep each night (7-8 hours for elderly). Actual sleep needs exist on a spectrum that is affected by genes (which determine not only how much sleep a person needs to feel rested but also at what times of the day they best fall and stay asleep), but this complex sleep system is not clearly understood. Many people claim to be alert on fewer than seven hours of sleep, but whether some individuals really do need less sleep is still up for debate.

Unfortunately, at least one third of adults (overall and in the elderly population age 60 or older) in the United States consistently report six or fewer hours of sleep on CDC surveys, and National Health and Nutrition Examination Surveys from 2005 through 2009. In the 40- to 59-year-old age range, 40 percent of surveyed adults slept less than the recommended hours.

Without adequate sleep on a regular basis, sleep deficits accumulate and compound existing health problems.

Despite the clear adverse effects of these sleep deficits and a better understanding of the complex interplay of hormones and the environment on the sleep cycle, treatment and self-care for insomnia remain notoriously unsuccessful.

CASE UPDATE

Your patient, A.H., received her flu shot and was amenable to your request to discuss the sleep aid (she is without kids for this visit). She tells you that she recently (two weeks ago) started working part-time in the afternoons and falls asleep quickly when she comes home at 8:30 p.m. However, since work began, she wakes at 1 a.m. every night and struggles to go back to sleep until her alarm goes off at 5 a.m. Thus, she is regularly missing out on the suggested minimum of seven hours nightly, so daytime insomnia symptoms are likely. What are your next counseling and assessment questions?

CAN PHARMACISTS ASSESS THE INSOMNIAC IN THE PHARMACY?

Unlike other mental health conditions, insomnia disorder is diagnosed and treated in large part according to patient-provided history that is guided by professional assessment questionnaires about health and behavioral habits. Informally, community pharmacists can play a crucial role in referring patients with symptoms of chronic insomnia to behavioral therapy or physician care and potential prescription therapy.

Asking a few simple questions during a short counseling session can identify triggers to insomnia and determine appropriate treatment options and referral needs.

Sleep problems can be as difficult to treat as they are to diagnose, in part because self-care is so prevalent. In one month, only 4 percent of U.S. adults reported use of prescription sleep aids. However, in 2013, OTC sleep aid sales were greater than $300 million dollars in the United States. Without health professional advice, adults skip important behavioral changes and potentially miss out on supervised, long-term prescription treatments. Early pharmacist efforts here can focus first on documenting habits and encouraging behavior change, then on selection of OTCs and referrals as needed for additional assessment and care (see table 1 and 2).

CASE UPDATE

A look at A.H.'s medications shows nothing new, but her meal, exercise, and sleep routines have become altered. She denies alcohol use or smoking and denies changes in her diabetes regimen. She used to sleep from 10:30 p.m. to 5:30 a.m. after an evening meal around 6 p.m. A.H. appears to be experiencing acute adjustment insomnia as a result of her changed work-life routine, but—because this new schedule is not a temporary lifestyle circumstance—the situation warrants assessment for behavioral treatment or medication to reset A.H. into a healthy sleep routine.

BEHAVIORAL TREATMENT OPTIONS FOR INSOMNIA

Patients who cannot fall or stay asleep should evaluate, with the pharmacist's help, their daytime and evening behaviors to adjust them and prepare a new sleep hygiene routine. Sleep hygiene refers to the choices and habits people observe to guide their bodies smoothly from wake to sleep states.

The body's sleep-wake cycle is extremely complex and involves hormonal controls, from melatonin to cortisol, serotonin, and gamma-amino-butyric-acid (GABA), from

Table 1. Identifying Potential Insomnia Triggers

Counseling Question	Reason for Sleep Disturbance
Purpose	Identify patients who might drink a night cap, smoke, exercise, or use tablets/computers in the evenings.
What medications do you take at night?	Determine stimulant use, medicines with short-term sedation only, and OTC factors.
What times do you last eat and drink before bed?	Identify patients who may be going to bed hungry, using alcohol to fall asleep, or trying to sleep too soon after a meal.
Do you have trouble falling asleep, staying asleep, or both?	Although prescription and OTC medicines are indicated for all types of insomnia disorder, the timing and selection of treatment are formed by the clinical experience and pharmacology of the choices.
How long has this problem lasted?	If acute, especially if fewer than 30 days, anxiety causes should be explored, and short-term hygiene recommendations and OTC treatment can be considered. If the problem is longer lasting, the patient should be referred to medical care regardless of recommendations for behavior change or OTC treatments.

Table 2. Insomnia Contributors and How They Disturb Sleep	
Contributor	**Reason for Sleep Disturbance**
Smoking	Stimulant effect when cravings start/nicotine wears off
Alcohol use	Short-term sedation only + abuse potential
Eating patterns	Too close to bed for body to relax or too early and hunger wakens patient
Exercise patterns	Within five hours of bed, acts as a stimulant
Work-life stressors	Increasing anxiety can delay or interrupt sleep
Medication timing	Sedatives that are short-acting can interrupt sleep later
TV/tablet use	Lights disrupt circadian rhythm and delay sleep

numerous body systems that continually send messages to the brain to be alert or at rest. Usually, an imbalance in at least one of these, if not multiple, triggers the onset of sleep problems like insomnia. The CDC and the NSF recognize the importance of personal actions to the release of these hormonal triggers and recommend ways to overcome sleep problems with good sleep hygiene choices.

To avoid triggering arousal signals before bedtime, patients with insomnia should reset their sleep habits with the following sleep hygiene adjustments:

- Avoid large night-time meals and caffeine but do not go to sleep hungry.
- Avoid alcohol, because it is an abuse risk but also because it induces sleep initially but may not prevent mid-cycle awakenings.
- Set one start time and end time for sleep and wake every day—regardless of the amount of actual sleep achieved at night—to adjust the body to a routine that encourages regular melatonin cycling along with light-dark triggers, too. Similarly, avoid midday naps even when tired, because they make it more difficult to fall and stay asleep at night. This type of sleep restriction can increase the body's likelihood of sleep when the new sleep schedule is observed regardless of fatigue.
- Avoid activities that stimulate arousal hormones or melatonin: any projects, even reading, performed in bright light should be tapered off in the evening before bedtime to encourage melatonin release. Watch exciting movies or television shows earlier in the evening, not right before bed, to avoid bright light and stimulation of arousal hormones, too.
- Avoid exercise, which stimulates cortisol and other arousal hormones, directly before bedtime. A better recommendation is up to 20 minutes of exercise around five hours before bedtime, to allow the body time to return to a resting state.
- For patients who experience awakenings, remove stimuli that release light and trigger anxiety, like such as LCD clocks, or at least move the stimuli away from a distraction-free zone near the bed. Sleep masks, sound machines, and other tools to counter the stimuli may help, too.

If insomnia has become a chronic problem, the missing restful hours from the accumulated sleep debt also should be replenished as much as possible. Pharmacists can help patients break down debt into smaller quantities that can be added to the recommended minimum of seven sleep hours. Alternately, using weekend or vacation time to refresh with extra sleep hours may be more appropriate with high deficits.

Establishing good sleep habits is the first step to insomnia treatment, before formal cognitive behavioral therapy (CBT) is tried. In the pharmacy, products that promote good sleep hygiene can be placed strategically near OTC sleep aids. For example, sleep masks and ear plugs can help patients who are distracted by external stimulation and can supplement better sleep habits, such as reducing external light before going to bed. Similarly, lavender oil, sound machines, or caffeine-free teas may encourage patients looking for medication to transition more gently from wakefulness to sleep.

When these efforts are not enough, professionally guided CBT and relaxation therapy may be needed, too. CBT is a disciplined approach of psychological care. When applied to insomnia, CBT provides a structured set of steps to help a patient reset sleep-related habits. Rates of successful treatment of insomnia with CBT are as high as 80 percent, and CBT appears equally effective to treatment with prescriptions like benzodiazepines. Relaxation therapy combined with changes to sleep habits is also supported by research evidence as an insomnia treatment. This type of CBT is particularly helpful to guide patients who have anxiety as a cause or result of acute or psychophysiological insomnia. Experts in CBT techniques often work in sleep centers accredited by the American Academy of Sleep Medicine. Pharmacists can suggest that interested patients ask their general practitioner to help them find such a facility.

SELF-TREATMENT OPTIONS FOR INSOMNIA

Although many people experience insomnia at least once in their lives, not many people consider visiting their prescriber right away. Pharmacists have the responsibility as the accessible health care provider at the site of OTC purchases to identify patients who need counseling for causes, treatments, and referrals of insomnia.

OTC Antihistamines

OTC antihistamines have an important role in overcoming the barriers to sleep, but they should not be used indiscriminately. These easily accessible sleep aids are recommended for short-term use only, in part because of their side effect profiles and in case a more complicated health condition is causing the sleep interruption. For example, if a patient with cancer pain comes to the pharmacy seeking a recommendation for a sleep aid, it may be more appropriate to assess and adjust their pain medications than to suggest an additional OTC product.

The antihistamine (H1 receptor blocker) drug class is the most common type of OTC medicine approved for insomnia treatment. Although second-generation antihistamines are used to treat seasonal allergy symptoms, all antihistamines have sedation or drowsiness as a main side effect. Older antihistamine products have higher rates of this adverse effect, so these drugs are selected for sleep aid formulations. Diphenydramine hydrochloride (25 or 50 mg) or citrate (38 mg) and doxylamine succinate (25 mg) are the most frequently used OTC antihistamines for sleep, found in a wide array of marketed products.

Antihistamines have a long history of safe use in adults, but some caution is suggested with these drugs:

- Because the drowsiness can be unpredictable and individualized, patients should avoid alcohol or other antihistamine use and should avoid driving or doing anything that requires alertness (such as slicing foods, cooking, operating appliances) when they use these sleep aids.
- Many marketed products contain acetaminophen or ibuprofen as well, which is unnecessary for patients without pain as a cause of their sleep disruption. These patients should try a different, single-drug formulation if possible, and any patient who takes a combination product should avoid taking additional acetaminophen or ibuprofen to avoid excessive dosing.
- Antihistamines should be used with caution in patients with asthma and in patients 65 or older, and they should not be used in patients with benign prostatic hyperplasia or angina because of the drugs' anticholinergic effects, such as increased heart rate and blood pressure and decreased urination.

Antihistamine sleep aids should be used only for 7-10 days, in part because tolerance to the sedative effect develops with continued use. More importantly, patients with continued symptoms after approximately two weeks of treatment should be referred to a physician for assessment of chronic insomnia.

Supplements

Supplements are touted as natural sleep aids; however, many of these marketed options are newer than—and have less research support than—diphenhydramine or prescription drug products. Also, herbal supplements remain unregulated in the United States and may not contain the ingredients that are claimed on the label. The United States Pharmacopeia independently verifies some brand names to provide ingredient quality control. If you, as the pharmacy owner/manager, have a preferred reputable USP-designated supplement line, melatonin, lavender, and valerian are treatment options with historical or documented efficacy for sleep disorders.

Melatonin products offer a synthetic version of the natural sleep-wake cycle regulator. Exogenous melatonin shortens the time to fall asleep and reduces the number of awakenings if taken at appropriate doses and times. Because its mechanism of action is so specifically related to the circadian rhythm, melatonin is best used in patients whose insomnia develops only as a result of a light-dark imbalance. An example beyond the traditional populations of shift workers or travelers is the patient with extended computer use at or past bedtime that has repeatedly delayed natural melatonin release.

OTC melatonin products claim to contain a variety of doses, from 0.2 mg to 5 mg. A dose of 1-3 mg increases blood levels from 1-20 times normal concentrations. Adults should use the lowest dose needed to induce sleep. Too much melatonin can cause headaches, nausea, dizziness, and irritability that further disrupt sleep. Pharmacists should recommend that any adult patient start with 0.2-mg doses and increase from there only as needed. Melatonin should be taken one hour before bedtime to simulate natural melatonin release.

A prescription receptor agonist of melatonin, ramelteon (Rozerem), was approved in 2005 to help patients who have trouble falling asleep. It is not used for nighttime wakenings. The 8 mg tablet should be taken 30 minutes before bedtime and works best when taken without food. Although ramelteon reduces the time it takes to fall asleep better than placebo, it is most appropriate in patients whose insomnia results from circadian rhythm disruption.

Melatonin supplements interact with diabetes medicines, warfarin, oral contraceptives, and more, so these products, although available to any patient, should not be considered safer than prescription medicines and should be used with health professional supervision. Melatonin has been used for up to three months for insomnia caused by circadian rhythm problems.

Many herbal products appear to induce relaxation and sleep although the mechanisms of action for the effects

are unclear. Products such as lemon balm or lavender may alter neurochemical regulators of arousal and relaxation or may simply contribute to soothing sleep habits. Lavender, a Mediterranean shrub, was used underneath pillows in folklore to prevent restlessness. Now, the flowers may be boiled for tea or its essential oil can be diluted for inhalation or massage. Lavender appears to increase sleep quality and reduce agitation by slowing the nervous system. Adding 1-2 drops to a tablespoon of a massage oil may be most effective for patients with insomnia secondary to back pain or tension. Up to four drops can be added to three cups of boiling water for inhalation, although this technique should be avoided in patients with lung problems, such as asthma.

Approved by the German Commission E, a regulator of herbal products in Europe, valerian has been used since the second century as a mild sedative. In the United States, valerian is generally regarded as safe, and it is believed to increase GABA and reduce anxiety much like benzodiazepines. Valerian can be used alone or in combination with other sedating herbs, but it does not appear to have an immediate relaxing effect. After a step-up period of almost two weeks, the full sleep benefits begin. Patients can try dissolving two to three grams of valerian root products (often preformulated into liquids with this dose in a single teaspoon) in one cup of boiling water for a calming tea. Valerian should be continued for 2-6 weeks. Side effects include headache and dizziness. A few patients may experience paradoxical anxiety and should not continue valerian use.

CASE UPDATE

You believe that the new sleep and meal pattern for A.H. are contributing to her insomnia, so behavioral changes should be enough to improve her sleep. Specifically, you recommend eating a small meal at or just after work and waiting until around 9 p.m. to go to bed. You also suggest that A.H. review her tablet and TV use and exercise routine and try to exercise before her part-time job (around five hours before she comes home for the night). A.H. plans to take a vacation next month without kids to catch up on sleep, so she is not very concerned about long-term sleep disturbance. However, she agrees to try the recommended behavioral options but would still like to use her OTC selection for two weeks before returning for another consultation. You ensure that she is not taking additional acetaminophen and agree to follow up with her then.

WHEN BEHAVIOR CHANGE AND OTCS AREN'T ENOUGH

Historically, insomnia that did not respond to behavioral or OTC treatment attempts had been treated with neuroactive drugs that caused side effects of sleepiness or drowsiness. Examples of first-line indications for these treatments ranged from depression and anxiety, to alcohol withdrawal and seizure disorders. When a side effect is used as the main reason for treatment, though, the other pathophysiological changes it causes are usually not required or desired.

The benzodiazepine class, which includes alprazolam, midazolam, diazepam, and more, offers short- and long-acting treatment of depression, anxiety, panic, and other mental health conditions. These drugs work by increasing the GABA effects at receptors in the brain to quiet excitation and induce sedation. The range of their effects depend on how broad or localized their GABA receptor actions are, but common side effects include dizziness, confusion, blurred vision, and poor coordination.

Low benzodiazepines doses such as alprazolam, with a half-life of 6-26 hours, are often used as sleep aids. Short-acting agents are preferred, because next-day drowsiness is less likely than with longer agents. Although benzodiazepines both hasten and maintain sleep, they are C-IV controlled substances that, with long-term use (more than one month), have a dependence risk. In older patients, benzodiazepines can also accumulate and cause daytime confusion and increased falls. Benzodiazepines are most appropriate for fast relief in adults with acute anxiety-related insomnia. Their mechanism of action is unlikely to address the cause of longstanding insomnia from physical or behavioral contributors, and chronic use increases the likelihood of withdrawal symptoms, such as irritability, panic and anxiety, nausea, heart palpitations, and cognitive difficulties.

Along with the benzodiazepines, a handful of other antidepressants or anti-anxiety agents, such as trazodone, may be used off label to treat insomnia. Like the benzodiazepines, lower doses are recommended (25-50 mg trazodone at bed time). Also like the benzodiazepines, these other neurologic classes work best for patients with existing anxiety or depressive disorders.

Newer Hypnotics

In 1992, a new type of prescription hypnotic was approved with an indication for insomnia treatment. Zolpidem (Ambien) is a GABA agonist in the central nervous system and was the first of a new class of neurologic drugs that selectively bind GABA-A receptors implicated in the sleep-wake cycle. Zolpidem is absorbed quickly, with peak concentrations after a mean of 1.6 hours with 5-10 mg doses, and an elimination half-life ranging from 1.4-4.5 hours. Zolpidem has been studied in acute and chronic insomnia and reduced the time it takes to get to sleep significantly better than placebo.

Zolpidem is available as a 5 mg or 10 mg tablet, and a cost-effective generic formulation was approved in 2007. An extended-release product (Ambien CR) is available to help reduce the number of night-time awakenings, but this product should only be taken if 7-8 hours of sleep time is available after the dose. Ambien CR should not be crushed or cut. An oral spray formulation of zolpidem, Zolpimist,

was approved in 2008 for patients to use like the regular-release tablet, right before getting into bed.

Along with zolpidem, eszopiclone (Lunesta) and zaleplon (Sonata) are hypnotics approved to treat transient or chronic insomnia. Like zolpidem, they should be taken directly before bed to avoid a risk of falls or accidents from drowsiness. Eszopiclone absorption peaks in just one hour, but the drug has a half-life of six hours. Like zolpidem, this medicine helps people fall asleep more quickly, but it also is recommended for patients who have trouble staying asleep. The starting dose of eszopiclone tablets is 1 mg immediately before bed, which can be increased to a maximum of 3 mg. However, elderly patients experience more than 40 percent greater exposure than other adult age ranges and should receive a maximum 2-mg dose. Next-day grogginess is more common with the highest dose and in elderly patients. Patients who take 3 mg should not drive or operate machinery the next day, even if they feel alert.

Zaleplon offers the shortest onset and duration of action in the non-benzodiazepine hypnotics class, with peak absorption within one hour and an elimination half-life of approximately one hour as well. When capsules are taken with a fatty meal, absorption is lower and is delayed by almost two hours. Age does not appear to affect zaleplon absorption or effects. Capsules are available in 5 mg, 10 mg, and 20 mg strengths and should be taken at the lowest effective dose, to reduce adverse effects, directly before bed. Zaleplon shortens the time to fall asleep in patients with acute or chronic insomnia, but it does not appear to improve sleep duration or the number of sleep disruptions.

Although the newer hypnotics have documented efficacy, they share some of the same safety concerns with benzodiazepines. Like benzodiazepines, these drugs are C-IV controlled substances. Dependence or addiction is possible, especially when used at high doses or for long durations. Withdrawal irritability or temporary rebound insomnia (perceived or documented) are possible after these medications are used for more than a few weeks. Like benzodiazepines, these drugs should not be used with alcohol or while driving, and daytime grogginess is possible particularly when a full 7-8 hours of sleep is not achieved. At higher doses, the hypnotic drugs can induce sleep activities, including eating, that occur without patient awareness. After any of these agents are prescribed, patients whose insomnia continues must be reassessed for potential physical or mental health causes of insomnia. These hypnotic agents opened the door to prescription therapies for insomnia but have not fully met patients' needs by focusing only on the role of GABA in sleep.

THE ROLE OF OREXINS IN THE SLEEP-WAKE CYCLE AND IN INSOMNIA TREATMENT

Orexins, also known as hypocretins, are small proteins that play a role in sleep and appetite sensations. First identified in the late 1990s, orexins are produced in the hypothalamus, and early research identified a link between abnormal endogenous orexin levels and narcolepsy, another sleep disorder. The presence of orexins activates brainstem and hypothalamic responses that maintain alertness or arousal (in part via norepinephrine, cholinergic, and histamine responses), so orexins are wake-promoting molecules. Orexins appear to interact with glucose and energy/metabolic cycles as well as with neurochemicals like acetylcholine and norepinephrine in sleep-wake cycles, so they might play a role in obesity, addiction, and stress in relation to and separate from their sleep disturbance role. Orexin release appears to be activated by metabolic changes such as low blood sugar, and higher levels of orexins stimulate physiologic changes, such as increases in heart rate and blood pressure, and higher levels of insulin and cortisol.

Suvorexant (Belsomra) is the first orexin inhibitor on the U.S. prescription drug market. Approved by the Food and Drug Administration in 2014, suvorexant is an orexin receptor antagonist indicated for adults who have trouble falling and staying asleep. The drug prevents the orexin alertness response to enhance the transition from wake to sleep and to minimize nighttime arousals.

In clinical trials, suvorexant appeared well tolerated. The drug peaks in the blood after approximately two hours and has a 12-hour half-life; it reaches steady state in three days. Doses should be taken within 30 minutes of bedtime and only if at least seven hours of sleep are possible after administration.

Suvorexant is metabolized by the CYP450 liver enzyme system and is a mild CYP3A inhibitor. Most drug interactions identified through this system have not required dose alterations; patients who take oral contraceptives, digoxin, or warfarin may be monitored to assess any possible changes in drug levels during suvorexant use, but dose adjustment is unlikely. Fluconazole, a CYP3A inhibitor, can increase suvorexant levels, though, so concomitant use should be avoided, or the lowest available suvorexant dose (5 mg) should be used, and the dose should not exceed 10 mg. Conversely, CYP3A inducers such as phenytoin or carbamazepine may lower suvorexant efficacy and require dose titration to effect.

Doses of 5 mg, 10 mg, 15 mg, and 20 mg of suvorexant are available in tablet form. Meals may delay the onset of action but are not contraindicated. The recommended starting and maintenance dose is 10 mg, and 20 mg is the maximum recommended dose for patients who tolerate the 10-mg dose but do not see improvement. Patients should use the lowest effective dose and should be reassessed after 7-10 days. If insomnia does not improve after use of the maximum dose, evaluation for other external causes is recommended.

Side effects associated with suvorexant are similar to placebo, except for increased rates of next-day sleepiness, confusion, or sleep activities (such as sleep walking or

talking). Tested doses of 30 mg and 40 mg were associated with more balance and next-day impaired driving problems than placebo, and were not approved. The approved 20-mg formulation also causes excessive daytime drowsiness and worsens next-day driving ability. Patients should not perform activities that require clear thinking within eight hours after a suvorexant dose—or during the day after taking suvorexant until they feel fully awake, especially if they did not meet the recommended minimum of seven hours set aside for sleep after taking a dose.

Although suvorexant works more specifically in the nervous system than broad GABA-active classes such as the benzodiazepines or hypnotics, and thus has potentially more localized actions, it was still approved as a C-IV controlled substance. The classification was based on the potential for human abuse of suvorexant as a marketed drug with similar effects, if not mechanisms, as established insomnia treatments, such as zolpidem. Clinical trials did not identify evidence of physical dependence, but overuse or abuse of suvorexant can lead to dangerous impairment of abilities (driving, concentration). The drug is prescribed with a patient medication guide that explains the risks of high or prolonged dose regimens.

CASE RESOLUTION

A.H. returns after two weeks and states that she has successfully adjusted her diet and exercise to earlier in the day and has started going to bed and getting up at the same times regardless of actual sleep hours. She sees a benefit in the routine but is still having trouble staying asleep and quieting her anxiety upon awakening. She does not like the OTC treatment, which makes her feel too groggy in the mornings when she is with her kids. She wonders if she should try melatonin or a prescription option. Because of her work shift, melatonin may be appropriate but should not be used indiscriminately or for long durations. You recommend that she visit a sleep center or her general practitioner to discuss combined CBT and prescription therapy and to look for causes in addition to the work schedule that may be contributing to the ongoing insomnia disorder. ■

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Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.

Continuing Education Quiz

Select the correct answer.

1. How does insomnia disorder differ from other mental health conditions?
a. It develops in a highly specific patient population.
b. It always resolves on its own, given at least three months.
c. Its diagnosis and sometimes treatment rely heavily on patient-reported history instead of testing.
d. Its treatments have low abuse potential and are effective within 7-10 days.

2. Which of the following statements is false?
a. Insomnia is one of at least 10 sleep-wake disorders described by the Diagnostic and Statistical Manual of Mental Health Disorders.
b. Insomnia can be defined as a sleep debt that results when a person chooses not to set aside adequate time for sleep.
c. Insomnia sometimes, but not always, leads to long-term sleep problems.
d. Insomnia often develops secondary to physical, mental, or lifestyle conditions.

3. Physical (not mental health) conditions that may contribute to insomnia development are:
a. High cholesterol
b. Major depressive disorder
c. Osteoarthritis
d. Family heart attack history
e. Two of the above

4. Which of the following medications can lead to sleep disruption and why?
a. Cetirizine at bedtime because of its drowsiness side effect interrupting the ability to stay asleep
b. Dextromethorphan at bedtime because of its drowsiness side effect interrupting mid-cycle sleep
c. Alcohol because of its stimulant effect when used right before bedtime
d. Nitroglycerin because of its extremely short duration of action to treat cardiovascular morbidity

5. Which of the following statements is true?
a. GABA is the only neurochemical known to affect the sleep-wake cycle as a sleep promoter.
b. GABA is one of many sleep-promoting chemicals and is the focus of prescription classes to treat insomnia.
c. Cortisol is a sleep-promoting hormone that closely follows the cycle of melatonin.
d. Cortisol awakens people mid-sleep because of the fight-or-flight response.

6. Which of the following activities may disrupt sleep by increasing cortisol release too late in the day?
a. Exercise just after lunchtime
b. Exercise just after dinner
c. An evening stress experience (such as a late work deadline, or illness onset)
d. Both B and C

7. Insomnia pathophysiology can be characterized in a simplified way as which of the following?
a. A state of excessive melatonin that induces sleep despite the wake-promoting activity of other hormones or molecules
b. An abnormal state of arousal that is triggered by the same neurochemical changes in everyone with chronic insomnia
c. A state of hyperarousal, when normal sleep promoting and wake promoting molecules are not balanced
d. A state of arousal triggered by GABA-inhibiting prescription drugs

8. Which questions are valid during pharmacy counseling sessions to assess the extent of insomnia?
a. What time do you go to work in the morning?
b. How often do you go out to eat in restaurants?
c. What time do you last eat or drink before bedtime?
d. How long has your sleep problem been happening?
e. Both C and D

9. Concerns about over-the-counter sleep aids include:
a. Lack of Food and Drug Administration oversight of products with two medications in one formulation.
b. Long-term use can lead to blackouts.
c. Only short-term use is recommended because driving becomes erratic after 7-10 days.
d. Only short-term use is recommended because longer-lasting insomnia warrants assessment by a health professional to identify secondary causes that can be treated instead.

10. Doses of lavender used today or in folklore include:
a. Taking 1-2 drops per tablespoon of oil as a massage treatment
b. Three drops in three cups of boiling water as an inhalant in patients without asthma
c. Dried flower sachets placed under pillows to enhance restfulness at bedtime
d. All of the above

11. Melatonin is considered:
a. A dietary supplement that is not regulated by the FDA.
b. A dietary supplement that also receives special FDA regulation.
c. A prescription drug used to reset circadian rhythms safely in adults and children.
d. A natural hormone that is not available as an external product.

12. Which of the following statements is true?
a. Taking more melatonin before bedtime increases the likelihood of staying asleep all night.
b. Melatonin release increases arousal and wakefulness.
c. Melatonin can be used for years without adverse effects in people whose light-dark cycle is upset.
d. Melatonin release is fairly consistent among adults, with a 9 p.m. release, and morning taper after 12 hours.

13. Benzodiazepines are the preferred first-line prescription treatment for insomnia because:
a. They are short-acting enough to prevent daytime grogginess.
b. They are not associated with withdrawal symptoms.
c. They are safe to use in all adult age ranges without contraindications.
d. None of the above.

14. The first non-benzodiazepine hypnotic to treat insomnia, _____, should be taken _____.
a. Zolpidem, at dinner time because of its longer time to peak absorption
b. Zalpelon, at bedtime because it is the only hypnotic with a risk of falls or accidents when taken earlier
c. Zolpidem, at bedtime because it is used to decrease the time to sleep onset
d. Zalpelon, at midnight awakenings, because there is still enough time to get a full night's sleep afterward

15. Because melatonin is a natural supplement, doses of 1 to 3 mg:
a. Are safe in any age population, because they increase blood concentrations only 1-3 times normal.
b. Can be taken regularly for up to one year without supervision, as melatonin is already found in the body.
c. Can be taken when people naturally go to bed, because it works immediately to induce sleep.
d. None of the above

16. A molecule identified in the 1990s, ____, plays a key role in the sleep-wake cycle by ____.
a. Orexin, reducing the levels of melatonin released by the pineal gland
b. Orexin, stimulating neurochemical systems of arousal and alertness
c. Melatonin, increasing the release of histamine, insulin, and cortisol in the brain
d. Glucose, by increasing appetite and reducing restfulness

17. Which of the following are appropriate doses of suvorexant in the given patient population?
a. A 5 mg starting dose in adults age 18 years or older with step-up to 10 mg dose after 7-10 days
b. A 10 mg starting dose in adults age 18 years or older with step-up to 20 mg maintenance dose after 7-10 days
c. A 10 mg starting and maintenance dose in adults age 18 years or older, with 20 mg reserved for well-tolerated but ineffective 10-mg trial (usually for 7-10 days)
d. A 20 mg dose for all ages with a warning about the risk of next-day drowsiness and driving impairment
e. Two of the above

18. Wake-promoting hormones:
a. Include GABA and cortisol, the two most studied molecules in insomnia pathophysiology.
b. Counteract the body's natural sleep-wake cycle by inducing a state of arousal instead of rest.
c. Block receptors in the central nervous system on a regular schedule to disrupt sleep at the same time each night.
d. Two of the above.

19. New hypnotic agents offer which advantages over benzodiazepines?
a. They are not controlled substances.
b. They do not cause daytime grogginess to the same extent.
c. There is at least one extended-release option that helps patients sleep sooner and longer.
d. They can be effective only at maintaining sleep.

20. Suvorexant is the first orexin-modulating prescription drug approved by the FDA, and it works by
a. Reducing orexin production in the brain.
b. Reducing orexin release at bedtime.
c. Blocking orexin release only in the presence of a fatty meal.
d. Blocking orexin activity at brain receptors that stimulate arousal.

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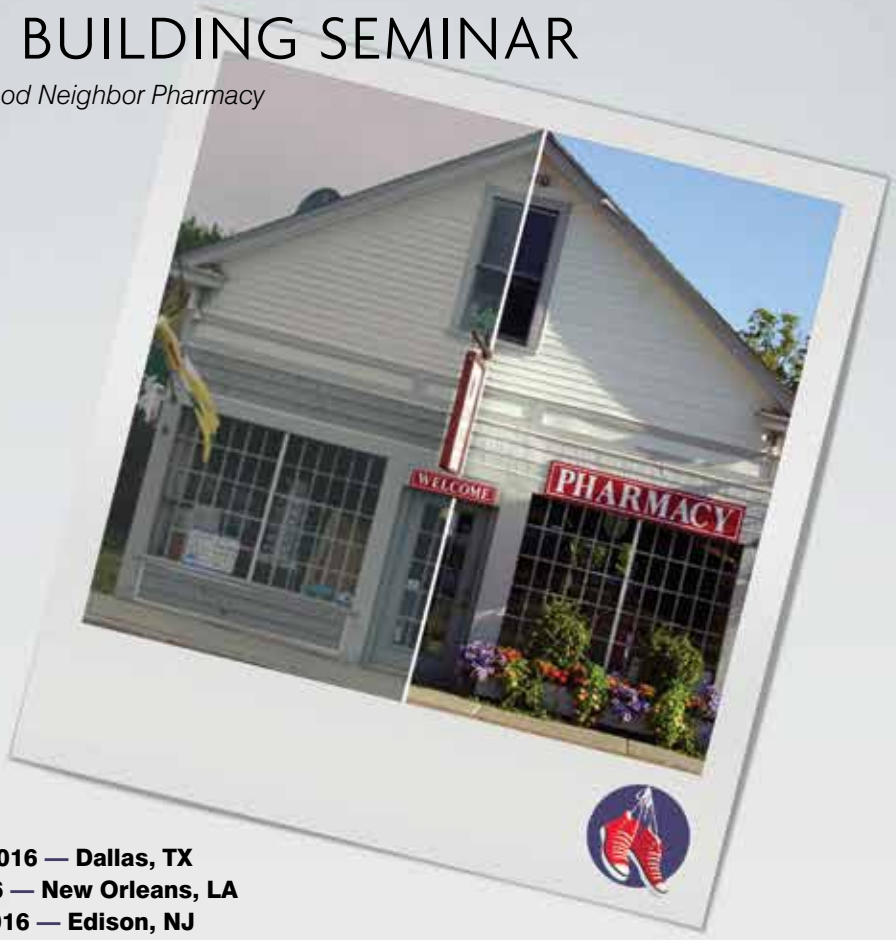

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Deciding to Sell Diapers

by Gabe Trahan

When deciding to add any new category or an extension of an existing one, you must ask yourself these three questions: Will it create measurable revenue? Will it attract new customers? And will it enhance my image? If you can answer yes to at least two of the questions, then you are safe to include the line in your inventory … unless the item is diapers.

> ***Before you pooh-pooh the idea of losing money on diapers, stop and look at your customer base.***

At best, diapers will only fill one of the above requirements, so you will have to decide if they are worth the space and investment. **To be successful in selling lots of diapers, you need to sell them below your cost.** That destroys the "create measurable revenue" goal. In the pursuit of attracting young moms and dads to shop at their locations, big box stores and sometimes chain pharmacies will feature diapers below the traditional pharmacy wholesale cost. Grocery stores will do this year-round. To them, it's like selling turkey at Thanksgiving for 49 cents per pound to get people in the door so they can sell other stuff (-ing).

Will selling diapers enhance your image? *Only if the price is right.* If you are a little high-priced on diapers, the only market you will sell to is individuals who haven't bought diapers in five years and are buying them for a one-time reason, such as a baby shower. Price your diapers 50 cents too high and you will never have a run on them. Diapers sold at the right price will help your pricing image; diapers sold at the manufacturer's suggested retail price will hurt it.

Will diapers attract new customers? In the end, it is the same answer for all three questions: only if you sell them below cost.

Before you pooh-pooh the idea of losing money on diapers, stop and look at your customer base. I've been in stores where the last person under the age of 30 who came in was lost and looking for directions. There is a reason why diapers are featured in sales fliers at recognizable low retails. If you want to attract parents of newborns and toddlers, you need to do a little more than just reduce the price. **Signage is key,** and the first sign should be placed outside by the road or on your digital marquee where everyone driving by can see it and act on it. Don't forget to mention it in print ads and social media and place your great diaper prices on the homepage of your website. Great prices on diapers are never kept a secret; just spread the word with signage and watch what happens.

When committing to a retail price for diapers, the next step is committing inventory and space. Running out of paper towels advertised at two for $3 is one thing; running out of the advertised diapers families need is another story. You will need a minimum 4-foot section (54 inches high) to be successful in the diaper business.

The ONLY exception to the golden pricing rule: If you are offering a great price on diapers, make sure to price the front of the package. Add a sign that yells the price. Remember, most people are not expecting you to have a good price on diapers – so remind them that you're different. ■

Gabe Trahan is NCPA's senior director of store operations and marketing. Gabe uses almost 40 years of front-end merchandising experience to help NCPA members increase store traffic and improve profits. Visit www.ncpanet.org/feo to watch videos, read tips, and view galleries of photo examples by Gabe. Follow him on Twitter @NCPAGabe for additional tips.

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